This book is inscribed to the memory of
two noble women of the past generation
Ro e D Ticarra
and
Catherine A Bell
Requescant In Pace

DISEASES *of the* THYROID *and* PARATHYROID GLANDS



BERNARD J FICARRA,
A B, Sc B M D, D S

Research Associate in Biology (Thyroid Physiology) Post-Graduate School Long Island University Associate Visiting Surgeon Kings County Hospital Center Associate Visiting Surgeon St Peter's Hospital Associate Visiting Surgeon Hospital of the Holy Family Formerly Associate Visiting Surgeon (Head and Neck Surgery) Brooklyn Cancer Institute Brooklyn N Y Consultant in Thyroid Surgery Yonkers Professional Hospital Yonkers N Y



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Dedicated to
the American Men of Medicine, Surgery and Research
Who Pioneered and Assisted in
the Elucidation Management and Treatment of
Thyroid Diseases

Contents

Foreword

SINCE KOCHER first focused the attention of the medical profession on the importance of treating goiter and other diseases of the thyroid gland surgically there has developed an ever increasing desire for knowledge concerning this subject

The unfortunate sequel of postoperative myxedema resulting from the first series of thyroidectomies by the father of thyroid surgery only stimulated the efforts to reduce the complications and improve the end results The discoveries of Cull and Kendall and of others added greatly to our knowledge of the functions of the gland but the surgical treatment of hyperthyroidism with its attendant dangers and mortality proved an ever increasing challenge The late Dr George Crile sought to reduce these hazards by the use of anoci association by packing the incision with flavine gauze and performing a secondary closure or by the use of sympathectomy of the adrenal glands It was Dr Miles Porter who injected boiling water into the substance of the gland to cause necrosis and destruction and thereby to lower its toxicity Others sought to accomplish more by the drastic use of weak solutions of carbolic acid and other solutions

Dr Charles Mayo and his associates depended largely on the careful selection of cases of toxic goiter for surgery the proper timing of surgery and in particular on the use of ligation and stage operations Despite these precautions patients continued to die Many died without the benefit of any surgery others following a stage operation and others who appeared to be good surgical risks following a thyroidectomy It was difficult and often impossible to predict which patient would develop a postoperative crisis There was no successful means of combatting or treating even the cases of postoperative crisis Intravenous feeding was yet to be discovered blood transfusions were only a little understood packing the patient in ice to lower his fever and quiet the delirium saved some the subcutaneous use of fluids helped others There was disagreement as to whether digitalis was helpful or harmful in combatting cardiac complications Some felt that the use of deep x ray therapy as advocated by Pfahler and others was preferable to surgery After years of study it became evident that this agent merely retarded the disease and that the lowered degree of hyperthyroidism continued to cause a serious and lasting damage to the cardiovascular system

Out of this maze of conflicting ideas and therapy suddenly came one of the truly great discoveries in the medical age When in 1922 Plummer suggested the use of Lugol s solution of iodine in the preoperative prepara

tion of cases of hyperthyroidism the surgical treatment of this condition was revolutionized Cases that formerly could never have gone to surgery were now so successfully prepared that thyroidectomy could be performed with little danger of the dreaded crisis occurring Further study however, was needed Crises still occasionally occurred and it soon became apparent that iodine was just as important in the postoperative as in the preoperative care

Then another sequela developed Because iodine was given to all types of goiters hyperthyroidism developed in certain nontoxic nodular goiters receiving the drug while cases of Graves disease long continued on therapy became iodine fast or resistant and when operated upon went into a crisis and died just as if they had never been treated

Finally it was shown that iodine had little or no benefit in patients having toxic nodular goiters As a consequence the risk of surgery in these cases was often great and no manner of postoperative therapy seemed to prevent the serious and occasionally fatal reactions

The improved surgical teamwork developed at the large goiter clinic namely the Mayo, Crile, and Lahey Clinics in this country, reduced surgical complications and lowered the mortality until it was less than 1 per cent in the cases of Graves disease

In 1941 Dr Astwood and his associates found the answer to the successful treatment of toxic nodular goiter Their discovery of thiouracil and subsequently of propylthiouracil tapazole and other preparations enables these cases to be treated so successfully that thyroidectomy could be performed with no greater risk than in the nontoxic cases In Graves disease these agents appear to have no particular advantage to iodine fast cases

Finally there came to the armamentarium of the thyroidologist radioactive iodine and at first it seemed that this agent might largely displace surgery in the treatment of goiter Soon it became evident that it had no place in the nontoxic nodular goiter it has no special advantage over the antithyroid drugs in the toxic nodular goiter it is helpful but not curative in malignant goiter It has been successfully used however in a large series of cases of Graves disease Whether in time I^{131} will displace surgery in the treatment of this disease only time will tell At most of the large thyroid clinics in this country thyroidectomy is still the method of choice after studying I^{131} for nearly ten years Its use has proven helpful as a diagnostic aid but it should be observed that hyperthyroidism is a progressive disease and if the diagnosis is not immediately apparent, the clinical signs and symptoms will soon become evident

The author of this book has had the opportunity of studying this subject in a large medical center for many years and is well versed in all its

various phases More especially he had the opportunity of studying under one of the finest of all American surgeons and a great student of thyroid the late eminent Dr Frank Lahey

Although progress in the development of our knowledge of this field has been slow, its course has from time to time been interrupted by brilliant contributions such as those cited and it is important that texts such as this keep the profession advised of the current status of the subject From a survey of the objectives and aims of the author and of the titles from the contents I am sure that this book will prove a helpful and valuable guide to all those who are interested in the field of thyroid surgery

ARNOLD S JACKSON M D
Madison Wisconsin

Preface

THE RECENT discoveries in medical science have materially changed the diagnosis and treatment of many diseases. This revolutionary evolution in the management of diseases is clearly illustrated in our modern treatment of thyroid disease as compared with methods used only a few years ago. The era of the antithyroid compounds and radioactive iodine is of very recent origin. The bringing together between the covers of one book of the most modern therapeutic methods in thyroid disease fulfills a very real need for the medical student, intern, resident, general practitioner, internist and general surgeon who encounters an occasional case of this malady. The thyroid specialist still sees quite frequently patients who are in serious difficulty because complications such as leukopenia, agranulocytosis and the "innocent" thyroid nodule which has metastasized were not recognized at their onset. This text will be an invaluable aid to all who treat diseases of the thyroid. It will enable the reader to have readily available an authoritative source book on "Diseases of the Thyroid and Parathyroid Glands."

Dr Ficarra's book is no mere compilation from previous texts. It finds its origin in his wide experience in the diagnosis and treatment of thyroid disease. From this experience he has chosen wisely and emphasized well the most necessary facts on this subject. There is no greater field for good management than in that presented by diseases of the thyroid gland. Dr Ficarra has done the profession a real service in emphasizing the importance of competent care for this group of patients.

I heartily recommend this book to all persons associated with medicine and surgery. All can benefit from the scientific and practical knowledge contained in the pages of this book. Anyone interested in the thyroid or parathyroid glands should have a copy of this book in his library. Everyone from the medical student to the thyroid specialist will not have completed his medical education until he has read this most excellent presentation on thyroid and parathyroid disorders.

WILLIAM TREVOR, M.D.
New York City, N.Y.

Introduction

THIS VOLUME on *Diseases of the Thyroid and Parathyroid Glands* has been published not because it is believed to contain any new revelations for the master thyroid surgeon but because it contains factual knowledge on thyroid diseases which should be made known to the general surgeon interested in thyroid surgery This book therefore is the literary product of a general surgeon who is interested in manages and operates upon patients with surgical disorders of the thyroid gland It is an accumulation of knowledge gained by an average general surgeon with an average surgical practice in an average American community

Many of the questionable phases in the management and treatment of thyroid diseases may not be acceptable to all those who may chance to read this book For example the technique described here should not be construed as the only procedure or the preferential routine of thyroidectomy It is the method to which I was initiated during my formal period of surgical training and therefore has become the technique to which I am accustomed Any technique of thyroidectomy which the surgeon finds satisfactory should be acknowledged as the method of choice for him

As in many other surgical matters an *open mind* and a right to express an opinion is an inherent attribute of the American surgeon This characteristic is reflected in the pages of this book namely that in many instances the written words are an expression of the author's opinions personal observations experiences and studies on thyroid diseases It is hoped that these observations and studies will be interesting and informative to those of my colleagues who may read this text

In the not too distant past a more distinct differentiation existed between the medical and surgical diseases of the thyroid gland At that time hypothyroidism was the chief medical disease Hyperthyroidism and neoplasms in their myriad form were considered to be surgical diseases of the thyroid gland However since 1941 as a result of certain new discoveries medical management has invaded the realm of surgical treatment for thyroid diseases Specific reference is made to the advent of the antithyroid drugs and radioactive iodine

Both the thiourea drugs and the isotopes have been used to treat hyperthyroid patients The success of these nonsurgical methods has been satisfactory so that it is proper to assume that more hyperthyroid patients are the recipients of these therapeutic agents than the surgeon realizes It is doubtful, however that these methods will completely eliminate the

services of the thyroid surgeon In this treatise therefore, consideration must of necessity be given to the medical regimen employed in the management of thyroid diseases Both of these medical methods will be discussed subsequently in their proper location

In addition emphasis will be placed upon some of the unusual aspects of thyroid disease Many of these are infrequently discussed in many thyroid presentations or have not been mentioned at all This present discussion will likewise emphasize certain other aspects of thyroid disorders which should be common knowledge to all those concerned with the treatment of thyroid patients

BERNARD I FICARRA, M D

1

Chronologic Résumé of Thyroid and Parathyroid History

1600 B C	Ancient Chinese used burnt seaweed and sponges in wine to treat goiter
1400 B C	In the Ayurveda of Sushruta (India) goiter is called galaganda It is attributed to derangement of the neck tendon
460–355 B C	Hippocrates considered goiter to be a deformity attributed to drinking of snow water
23–79 A D	Pliny the Elder Roman maintained that goiter is caused by impurities in the water
25–50	Celsus refers to the dangerous operations for the removal of a goiter in his De Struma (Opera Lib VIII)
130–200	Galen wrote of the two neck glands in which moisture is generated are of spongy nature and from them the humor oozes out and trickles down there being no necessity for ducts Thus he described the hormonal function of the thyroid gland Galen thought that the thyroid secretion lubricated the larynx
560	Aitius regarded exophthalmic goiter as a variety of aneurysm
629–690	In the Books of Paul (Paulus Aeginetus) reference is made to the fact that in those days physicians still used the term bronchocele for goiter
944	In the Royal Book of Holy Abbas (Persian) we are informed that For goiter in which medication is of no avail surgery is necessary
1013–1106	Albucasis mentions an operation for goiter which disease he calls elephantia is of the throat
1136	In the Persian system of medicine (Jurjani) attention is called to the concurrence of exophthalmos and goiter
1170	Roger of Salerno alluded to goiter and scrofula and recommended their treatment with sponge ashes

1235–1311	Arnold of Villanova suggested burnt sponge and seaweed to treat thyroid diseases
1271	The earliest reference made by an Occidental writer to goiter in China is recorded by Marco Polo in his travelogue He wrote 'They are in general afflicted with tumors on the throat occasioned by the nature of the water which they drink '
1418	Valescus de Taranta popularized the treatment of goiter as advocated by Arnold of Villanova in the previous century
1452–1519	Leonardo Da Vinci stated that the thyroid glands (he thought there were 2) were made to close the gaps where the neck muscles were absent, and that the thyroid separated the trachea from the clavicle
1520–1575	Eustachius termed the thyroid glandula laryngea and applied the name isthmus to the part connecting the two lobes
1543	The great anatomist Vesalius described the thyroid as 2 glands one on each side of the root of the larynx which secrete a humor
1563	Realdo Columbus pointed out for the first time that the thyroid gland normally was relatively larger in women than in men
1601	Giulio Casserio described the thyroid as a single organ consisting of 2 parts He concluded that this gland had no secretory effects
1602	Felix Plater referred to cretins in connection with mental deficiency
1619	Fabricius d Aquapendente was the first to localize the thyroid gland as the anatomical seat of goiter
1657	Hoefer discussed the causation of goiter by air water and food
1657	The term bronchocele was used by Paul Aeginetus (from the Greek meaning windpipe) as a synonym for goiter is recorded in English for the first time in A Physical Dictionary '
1659	Thomas Wharton did not clearly distinguish the thyroid from the submaxillary glands but he called it thyreoidea from the Greek meaning an oblong Shield ' He

believed the thyroid gland dried up the superfluous moisture from the recurrent nerve

1665 Malpighi was the first to investigate the internal structure of the thyroid gland

1698 William Cowper concluded that the thyroid had the same 'office' as the thymus

1711 Vercellani of Asti stated that the thyroid was a receptacle for worms

1717 Heister refutes the postulate of Vercellani

1750 Lalouette first called attention to the minute structure of the thyroid gland by stating that the vesicles seem to communicate with each other

1776 Haller classified the thyroid as a ductless gland pouring a specific fluid into the veins and so into the general blood circulation

1779 The word Hypothyroidism appears in the Oxford Dictionary

1786 De Saussure ascribed cretinism to the concentrated air in deep valleys rather than to water

1786 Parry described the first recorded case of the symptoms corresponding to the syndrome of hyperthyroidism

1789 Vincenzo Malacarne published the first important book on endemic goiter

1792 Pierre Desault isolated and ligated the superior and inferior thyroid arteries before cutting them and was apparently the first to dissect the firmly adherent gland from the trachea

1800 Antonio Testa reports the prominence of the eyes and the cardiac symptoms in hyperthyroidism

1802 Flajani reports the case history of a young Spaniard with severe hyperthyroidism listing the symptoms accurately without realizing the true significance of the three main symptoms

1811 Bernard Courtois discovers iodine

1813 Sir William Blizard performs the first thyroid artery ligation on man

1815 Sir Humphrey Davy discovers iodine in marine products

1820 Coindet of Geneva suggests that the beneficial effects in

	treating goiter with marine products might be due to the iodine
1824	Angellini found iodine in certain natural springs which were known to cure goiter
1827	Sir Astley Cooper described his experimental thyroidectomies the first to be performed in England
1829	Magendie presents to the Royal Academy of Science 'the motives which have induced M Lugol to employ an aqueous solution of iodine'
1835	Robert Graves first presented a full picture of exophthalmic goiter recognizing the rapid heart, protruding eyes and nervousness as well as the enlarged thyroid
1836	P J Roux reports in the Paris Archives of Medicine a case in which a goiter was removed surgically The operation was performed on March 26 1835
1840	Carl Von Basedow of Merseberg described the classic symptoms of hyperthyroidism which gave rise to the 'Merseberg triad' The triad is thyroid enlargement, exophthalmos and tachycardia
1846	Robert Liston gave his opinion to be that tumors of the thyroid should be treated surgically
1848	Diffenbach states the operation for goiter is one of the most thankless most perilous undertakings which if not prohibited should be restricted
1849	Prevost suggests that goiter was due to iodine deficiency in drinking water He suggested that the iodine in certain salts protected against goiter
1850	Luigi Porta ligates the thyroid arteries to produce ischemic atrophy of the gland
1851	Victor Von Bruns successfully removes several thyroid nodules
1854	William Stokes describes hyperthyroid heart disease
1855	Kaestl proposed the use of iodized salt to prevent goiter
1859	Moritz Schiff concludes that the thyroid gland had an internal secretion
1859–1876	Chatin establishes that goiter and cretinism are due to the absence of iodine in the drinking water and in the air
1860	Rilliet gave the French Academy of Medicine his classical description of iodine toxicity

1863	Charcot describes tremor of the hand as a sign of exophthalmic goiter
1864	Friedrich Wilhelm Albrecht von Graefe describes the failure of the upper lid to move downward promptly and evenly with the downward movement of the eyeball often seen in hyperthyroidism with exophthalmos
1870	An advance in the use of hemostatic forceps occurs at the Schieberpvorrichtung of Fricke The efficient control of hemorrhage by means of the hemostat replaced the crude cautery the artery hook the ligature carrier the mass ligature and the crushing forceps
1875	Austin Flint states from the point of view of physiology the thyroid gland may be removed without interfering with any of the vital function
1879	Halsted popularizes the use of the hemostatic forceps in America
1880	Parathyroid glands discovered by Sandstrom
1883	Kocher and Reverdin described the effects of total excision of goiter in 100 patients
1883	Sir Felix Semon puts forward the view that cretinism myxedema and postoperative myxedema were all due to thyroid insufficiency
1883	Bubnow begins a chemical investigation of the thyroid
1885	Boeckel is the first to use the thyroidectomy transverse collar incision in the normal lines of skin cleavage
1886	Sir Victor Horsley in *Lancet* advances the theory of the thyrogenous origin of exophthalmic goiter asserting that the thyroid body is first affected and that all the symptoms are explainable by an altered function or dysthyroidism
1889	Biondi (with Heidenhain) establishes histologically that both the thyroid and parathyroid glands are secreting glandular organs
1890	American surgeons commence to operate for thyroid disease The leaders in this field are W S Halsted C H Mayo and G W Crile
1891	Brown—Sequard with D Arsonval described 'chemical messengers which in later years are called hormones
1891	Murray uses an extract of the thyroid gland to treat a patient with hypothyroidism

1891 Von Recklinghausen describes the autopsy bone findings in osteitis fibrosa cystica

1892 MacKenzie and Fox independently record their success in the administration of thyroid preparations

1892 Gley describes the importance of the parathyroid glands

1893 Kocher postulates that iodine most probably occurs in the thyroid and is its most fundamental constituent

1895 E Baumann confirms the presence of iodine in the thyroid gland

1895 At first regarded as accessory thyroids, the parathyroids are stated by Kohn to be anatomically and physiologically distinct from the thyroid

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1895 George W Crile Sr introduces his theory of anoci association for the reduction of surgical shock This lessened the surgical mortality of toxic thyroid patients and instituted the era of stealing the thyroid under narcosis

1896 Hutchinson discovers that iodine of the thyroid gland is bound to a globulin

1896 Riedel of Jena describes ligneous thyroiditis

1896 Vassale and Generali show that the parathyroids have a function distinct from the thyroid

1898 Kocher establishes a definite procedure for thyroidectomy and popularizes the incision of Boeckel which in later years is called the Kocher incision

1899 Oswald attempts to chemically isolate the thyroid principle

1900 Vassale and Generali elucidate the function of the parathyroid glands and described postoperative tetany

1907 Erdheim, the pathologist, associates parathyroid tumors with skeletal decalcification

1908 MacCallum shows that tetany in parathyroidectomized dogs is due to a lowered blood calcium

1909 Emil Kocher receives the Nobel Prize for medicine At this time he had operated upon more than 9 000 patients His mortality was less than one half of 1%

1909	Dunhill of London points out that thyroid heart disease can be cured by thyroidectomy
1912	Hashimoto describes struma lymphomatosa
1915	Charles De Sajous advances the hypothesis that hyperthyroidism was due to: A severe mental stress, fear, rage or grief—which cause an excessive catabolism etc. Thus he calls attention to the psychic component of hyperthyroidism
1915	David Marine and associates find that living thyroid tissue has an affinity for iodine and that it is rapidly stored in the gland no matter how the iodine is given
1916	Binger and Fitz attempt to produce exophthalmic goiter experimentally (Am. J. Physiol.)
1917	Kendall of Mayo Clinic calls the chemical substance in thyroid Thyroxine and isolates it from the thyroid
1919	Emil Goetsch becomes Professor of Surgery at Long Island College of Medicine and establishes the first thyroid service in Brooklyn, New York
1923	Plummer and Boothby publish their investigations on the use of iodine in hyperthyroidism. This gave a great stimulus to the surgical treatment of hyperthyroidism
1924	Hanson isolates the parathyroid hormone
1925	Felix Mandl of Vienna proves the true nature of parathyroid adenoma
1926	Collip prepares a parathyroid extract that can raise blood calcium
1926–1930	Harington of London isolates and crystallizes thyroxine. He proves that the molecule contains 4 iodine atoms attached to 2 aromatic rings
1926	Abelin observes that the toxic effects due to feeding thyroid gland to rats could be lessened by diets rich in cod liver oil or egg yolk
1927	Lahey Clinic is founded in Boston by the late Dr. F. H. Lahey, whose staff has made noteworthy contributions to the management and surgical treatment of thyroid diseases
1936	De Quervain describes a form of thyroiditis which now bears his name
1943	Astwood and others introduce the thiouracil drugs in the treatment of hyperthyroidism

1891	Von Recklinghausen describes the autopsy bone findings in osteitis fibrosa cystica
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2

Anatomy and Physiology of the Thyroid Gland

Brief Anatomic Review of the Thyroid Gland

THE THYROID is the largest ductless gland of the endocrine system in the human body. It is situated below the thyroid cartilage frequently referred to as Adam's apple in front of the neck. From an anatomical viewpoint it consists of two lateral lobes each of approximately equal size and shape flat in character and simulating the general configuration of a Brazil nut. The lobes are commonly referred to as the right and the left one of each lies on either side of the upper part of the trachea. A rather narrow band of thyroid tissue connects these two lobes and this band is commonly called the isthmus of the thyroid. The isthmus lies across the trachea covering the second third and fourth cartilaginous rings of the trachea. There is an additional lobe called the pyramidal lobe in about 50 per cent of the individuals. It is also referred to as the pyramid of Lalouette. The pyramidal lobe arises from the upper border of the isthmus and runs in a long narrow strap-like process superiorly toward the hyoid bone. When the thyroid is viewed anteriorly the entire gland roughly simulates the letter U. The weight of the normal human thyroid gland varies in the adult male from 20 to 60 gr. It is somewhat heavier in the adult woman.

There are two types of tissue substance which compose the glandular structure, namely the essential secretory elements known as the parenchyma and the fibrous connective tissue which encapsulates these elements and in reality is the supporting framework of the gland itself. The functional tissue or the parenchyma consists of numerous very small rounded chambers which have been given various terminologies. These chambers are commonly described as follicles, vesicles, acini or alveoli. Each of the oval chambers has an interior lining composed of a single layer of epithelial cells. They are filled with a viscid fluid called the colloid which contains the active secretion of the gland. These lobules are independent units which secrete individually and are separated from each other by fine strands of connective tissue. Minute capillary blood vessels which can be found in these strands transport the glandular secretion

1944 Oliver Cope of Boston describes the Delphian node associated with thyroid cancer

1946 Radioactive Iodine is prepared at the Atomic Research Plant at Oak Ridge, Tennessee and is made available to the medical profession for diagnosis and treatment of thyroid disease

1951 J Gross and Leblanc discover a hitherto unidentified iodine-containing compound in human plasma which has been identified as 3 5 3 1 triiodothyronine

1953 *Gross and Pitt Rivers find that synthetic triiodothyronine* is active in preventing goiter in thiouracil treated rats and duplicates the effects of thyroxin on body growth kidneys, etc

1953 Jaffe reports 80% satisfactory remission in 1 720 recorded cases of hyperthyroidism treated with radioactive iodine

1954 Tobey Levitt of London publishes a masterful treatise on the thyroid gland which correlates in one volume the scattered knowledge of thyroid diseases

1954 Wilkinson and associates suggest that triiodothyronine may be the metabolically active form of the thyroid hormone This belief gains support from the fact that the compound butyl 4 hydroxy 3 5 diiodobenzoate depresses the biological activity of thyroxin but enhances that of triiodothyronine Since this compound depresses the urinary iodide after the injection of diiodotyrosine and of thyroxin it is postulated that its inhibitory effect on thyroxin is due to a restraining effect on the deiodination process In turn this restraining effect by retarding the breakdown of triiodothyronine extends its period of effective biological action

2

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into larger vessels enmeshed in the stroma From these vessels the thyroid secretion is poured into the major blood vessels

If a section of the normal thyroid gland is placed under a microscope there is immediately seen an arrangement of follicles which vary considerably in size This size may be anywhere from one millimeter in diameter to the smallest visible follicle of about 20 microns The epithelial cells lining the follicles are cuboidal in shape each having a round nucleus with



Fig 1 The thyroid gland is a highly vascular organ situated at the front and sides of the neck It consists of a right and left lobe connected in the central areas by a narrow portion called the isthmus A pyramidal lobe is present occasionally and arises from the upper part of the isthmus or from either lobe The thyroid gland overlies the upper trachea and rests close to the inferior borders of the thyroid cartilage and some of the extrinsic muscles of the larynx

a well marked nucleolus These cells contain filamentous processes (mitochondria) situated at the inner edge of the cells near the colloid containing lumen The filamentous processes are considered by some investigators as indicators of cellular glandular activity They are conspicuous during the active secreting phase and are seen with difficulty when the gland is quiescent When the thyroid gland functions normally almost all the follicles contain colloid which is densely packed within the acinus It is common to see under the microscope small colloid free vacuoles in the thyroid gland which are more marked at the periphery of the colloid mass Very often this is most noted opposite the free surfaces of individual epithelial cells

Physiology of the Thyroid Gland

The thyroid gland is not essential as a physiologic organ but it is necessary for the maintenance of health Its active hormone is called thyroxin (tetraiodothyronine) Thyroxin appears to be the active group of iodo

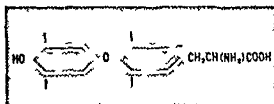


Fig 2 Structural formula of thyroxine When thyroxine was identified chemically it then became necessary to synthesize it in the laboratory In 1926 this was accomplished and the structural formula was clearly identified and demonstrated (Courtesy of Warner-Chilcott Laboratories)

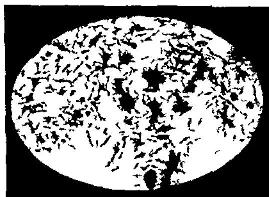


Fig 3 Crystalline form of thyroxine This photomicrograph of synthetic L-thyroxine is magnified three hundred times (300 ×) (Courtesy of Warner-Chilcott Laboratories)

thyroglobulin which is considered by many physiologists to be the true thyroid autocoid however since thyroxin is the active segment, it is acknowledged to be the thyroid hormone When thyroid extract is given to an experimental animal or to a human being it is taken up by the thyroid gland stored there and firmly bound therein This is an immediate process

Under physiologic activity the function of the thyroid gland is to manufacture thyroxin Thyroxin in turn has the function of maintaining the metabolic rate By means of its varied activity it alters the metabolism

into larger vessels enmeshed in the stroma From the vessels the thyroid secretion is poured into the major blood vessel

If a section of the normal thyroid gland is placed under a microscope there is immediately seen an arrangement of follicles which vary considerably in size This size may be anywhere from one millimeter in diameter to the smallest visible follicle of about 20 microns The epithelial cell lining the follicles are cuboidal in shape each having a round nucleus with



Fig 1 The thyroid gland is a highly vascular organ situated at the front and side of the neck It consists of a right and left lobe connected in the central areas by a narrow portion called the isthmus A pyramidal lobe is present occasionally and arises from the upper part of the isthmus or from either lobe The thyroid gland overlies the upper trachea and rests close to the inferior borders of the thyroid cartilage and some of the extrinsic muscles of the larynx

a well marked nucleolus These cells contain filamentous processes (mitochondria) situated at the inner edge of the cells near the colloid containing lumen The filamentous processes are considered by some investigators as indicators of cellular glandular activity They are conspicuous during the active secreting phase and are seen with difficulty when the gland is quiescent When the thyroid gland functions normally almost all the follicles contain colloid which is densely packed within the acinus It is common to see under the microscope small colloid free vacuoles in the thyroid gland which are more marked at the periphery of the colloid mass Very often this is most noted opposite the free surfaces of individual epithelial cells

Physiology of the Thyroid G

The thyroid gland is not essential as a physiologic
sary for the maintenance of health Its active horm
(tetraiodothyronine) Thyroxin appears to be the

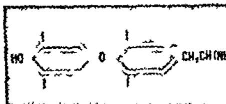


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thyroid autocoid however since thyroxin is the
acknowledged to be the thyroid hormone When t
to an experimental animal or to a human being it

in accordance with the changing body physiology Iodothyroglobulin (through its active chemical group, thyroxin) accelerates the oxidation of proteins fats and carbohydrates It also increases the elimination of calcium and magnesium Thyroxin acts directly on the cardiac muscle to produce tachycardia Tachycardia continues even after thyroxin ceases to be administered and stops only after the effect of the hormone has been dissipated Experimentally a thyroxin stimulated rabbit s heart continues to have tachycardia for several hours even after the heart has been placed in Ringer Locke solution

A diminution in thyroid secretion due either to inadequate iodine intake or partial thyroidectomy results in a compensatory hypertrophy of the gland The immediate causative factor for this hypertrophy is the antuitary thyrotrophic hormone from the pituitary gland Parenteral injection of the antuitary thyrotrophic hormone will produce a compensatory hypertrophy similar in character to that seen in the thyroid remnant following partial thyroidectomy The thyroid and antuitary glands are intrinsically allied to each other

When there is an insufficient systemic thyroid hormone the antuitary is stimulated to manufacture more thyrotrophic hormone in order to replenish the deficit When an adequate quantity of circulating thyroid hormone is produced the antuitary is inhibited and the thyrotrophic hormone is no longer produced to stimulate the thyroid gland In the etiology of toxic goiter both thyroxin and thyrotrophic hormone plus all those factors which affect these hormones must be considered and evaluated

Exophthalmic goiter and goiter without exophthalmos are the results of excessive secretion of antuitary thyrotrophic hormone In exophthalmic goiter the antuitary is stimulated by an unknown factor In hyperthyroidism without exophthalmos the antuitary is overactive because there is an insufficient thyroid secretion so that the inhibiting mechanism blocking the secretion of the thyrotrophic hormone is not available Irrespective of the innumerable theories advanced in the etiologic discussions on hyperthyroidism one factor always remains This factor is the antuitary thyrotrophic hormone the indispensable agent which produces the increase in thyroid gland activity

The destination or end point of the thyrotrophic hormone is the parenchyma of the thyroid gland When this hormone arrives at the thyroid gland certain things take place What exactly occurs is not definitely known however there is available a certain amount of evidence which leads one to suppose or presuppose what does happen This activity is more easily interpreted if one thinks in terms of what is actually known of the thyroid gland functions These functions concern themselves with the manufacture of the thyroid hormone and are identified as

1 A mechanism for trapping iodide from the blood stream
2 The synthesis of thyroxin which involves the iodination of tyrosine to diiodotyrosine and the coupling of two molecules of the latter to form thyroxin. These reactions take place within the chain molecule of thyroid protein called thyroglobulin
3 The storage of the hormone as thyroglobulin within the thyroid follicles
4 The discharge of the hormone into the body itself via the blood stream

A study of the action of the thyrotrophic hormone is facilitated by the fact that certain drugs are available which are capable of separating these several thyroid functions. Potassium sulfocyanate blocks the trapping mechanism. Another drug which can do this is perchlorate and certain other anions. Thiouracil and other drugs of this family interrupt the synthetic mechanism. Thyrotrophic hormone probably promotes all the functions of the thyroid but when only a part is blocked it will accelerate the unblocked thyroid physiology. Thus the gland blocked with thiouracil will still trap iodine when the thyrotrophic hormone is administered. It will also liberate the hormone. In view of the fact that the synthetic mechanism is blocked this must indicate that thyrotrophic hormone promotes the breakdown of stored thyroglobulin. The physiological release of the hormone may be the earliest effect of thyrotrophic hormone on the thyroid gland. Investigative work of DeRobertis suggests that this release is due to almost immediate activity of the proteolytic enzyme system of the thyroid gland[96]. This immediate activity brings about a reduction in the molecular size of the stored protein and permits the thyroxin containing fractions to escape into the circulation. Hypertrophy and hyperplasia of the thyroid parenchyma then occurs with an increased trapping of iodine. Finally 48 hours or more after the injection of thyrotrophic hormone an increased synthesis of the hormone results

It may be well to ask what the thyroid gland itself does to thyrotrophic hormone while the above activities are taking place. Rawson and his associates have shown that when thyrotrophic hormone acts on the thyroid gland it (thyrotrophic hormone) disappears[137, 143]. This disappearance however is not due to destruction because hormone activity can be restored by heat or by certain mild reducing agents. The hormone is merely inactivated but retains its capability of reactivation. The hormone may be found in the urine in its inactivated form and under certain circumstances it has been found in its active form as well

The close relationship between the pituitary and thyroid glands has been spoken of as the *Pituitary Thyroid Axis*. This term first employed

Biochemistry of the Thyroid Gland

The synthesis of the thyroid hormone has been discussed rather briefly in previous paragraphs Specifically, it must be recalled that, in 1944 Harington actually formulated the various steps of thyroid hormonal synthesis in vivo [6] These steps are

1 Concentration of iodide in the thyroid gland
2 The oxidation of iodide into iodine
3 The iodination of tyrosine to diiodotyrosine
4 The coupling of two diiodotyrosine molecules to form thyroxin

A more recent work (Gross and Pitt Rivers) has identified a new iodinated amino acid as a normal constituent of human plasma and of the thyroid gland [33] This new amino acid (3 5 3 triiodothyronine) is more active than L thyroxine in preventing thiouracil induced goiter in rats It is at least as active as L thyroxine in restoring the basal metabolic rate and blood cholesterol of myxedematous patients to normal levels (1952) These findings lead to the consideration of a further step in the synthesis of the thyroid hormone To the previously mentioned four steps one should now add the fifth

5 The formation of triiodothyronine

It is possible that triiodothyronine may be formed by enzymic dehalogenation in the thyroid as well as in other tissues It must be remembered that the amount of triiodothyronine present in the thyroid gland is very small compared with the amount of thyroxin in the gland It is therefore possible that more sensitive methods for the detection of dehalogenation are required than have been used previously The entire question of the biosynthesis of triiodothyronine is not settled at this time

Hydrolysis of Thyroglobulin in the Thyroid Gland

It has been mentioned previously that the thyroid gland possesses a proteolytic enzyme This enzyme can be demonstrated in the follicular colloid extracted from the thyroid gland of experimental animals The proteolytic activity of this enzyme can be increased after the administration of thyrotrophic hormone Similarly it can be decreased following the administration of iodine This enzyme activity varies in different pathological conditions in humans In patients with severe toxic goiter, it is increased to twice the normal activity In patients with simple colloid goiter it is lowered

Gross and his associates have shown that the thyroid contained small amounts of free iodinated amino acids which could be extracted with butanol from the thyroid gland without previous hydrolysis These free iodinated amino acids have been identified as

1. Monoiodotyrosine
2. Diiodotyrosine
3. Thyroxine
4. Triiodothyronine

The ce are presumably formed by proteolysis of thyroglobulin

In reference to monoiodotyrosine and diiodotyrosine neither one of these amino acids have been found in the circulation In 1951 investigators demonstrated that the thyroid gland possessed an enzyme system which was able to dehalogenate both mono and diiodotyrosine[33] It was further found that the dehalogenase was not inactive towards the iodinated tyrosines when they were bound in thyroglobulin Therefore only free amino acids could be attacked by the enzyme dehalogenase The metabolism of the iodinated tyrosines therefore can be regarded as taking place entirely within the thyroid gland after proteolysis from thyroglobulin They are completely dehalogenated and the iodide formed can be utilized again for the cycle of thyroid hormone synthesis Furthermore it has been shown that the activity of the enzyme is not destroyed with the destruction of the thyroid cell and thyroid extracts have been found to be active It appears that this particular enzyme is active only on halogenotyrosine

Circulating Thyroid Hormone

The fate of thyroxine and triiodothyronine after their proteolytic release from thyroglobulin has been the topic of much speculation The question advanced was whether the circulating thyroid hormone was a simple amino acid a peptide or a polypeptide of thyroxin or thyroglobulin itself In 1948 Taurog and Chaikoff (quoted by Gross) produced a large amount of evidence substantiating the contention that the plasma hormone was thyroxin This work received confirmation by others (e g Laidlaw) and it became generally accepted that thyroxin alone was the circulating hormone

Our present knowledge of the high thyroidal activity of triiodothyronine requires that it should be called the thyroid hormone The sequence of events leading to the appearance of the hormone in the blood can be outlined as follows

1. Synthesis of thyroxine and triiodothyronine in the thyroid (either simultaneously or consecutively)
2. Liberation of thyroxine and triiodothyronine from thyroglobulin by proteolytic hydrolysis
3. Passage of thyroxine and triiodothyronine from the thyroid into the circulation

It cannot definitely be stated whether thyroxin is the precursor of tri

iodothyronine in the thyroid gland and is itself physiologically inactive, or whether both compounds possess independent activity in their relation to each other. Until the sequence of events leading to their synthesis in the thyroid gland and their respective activities on the structures outside of the thyroid gland are more accurately understood the circulating thyroid hormone may be regarded as composed of both of them.

Summary of Recent Knowledge of Biochemistry of the Thyroid Gland

1. The three main biochemical functions of the thyroid gland are:
(a) The collection of iodide from the plasma.
(b) The transformation of iodide into organically bound iodine.
(c) The release of the hormone into the circulation.

2. There are various factors controlling the synthesis of the thyroid hormone and experimental evidence has been accumulated substantiating the nature of this synthesis to be enzymatic or a simple chemical reaction.

3. The pituitary gland exerts a powerful influence in the synthesis of the thyroid hormone. Recent evidence has been offered on the independent action of thyrotropin on the iodide concentrating mechanism and the organic binding of iodine.[33] There is conflicting evidence as to whether the pituitary actually controls the organic fixation of iodine or merely accelerates the reactions involved in this process.

4. As to the fate of iodinated amino acids in the thyroid, it is believed at present that monoiodotyrosine and diiodotyrosine do not leave the thyroid gland after proteolytic hydrolysis of thyroglobulin but are enzymically deiodinated with the formation of iodine. This iodide is available for re-utilization in hormonal synthesis. Thyroxine and triiodothyronine are released into the circulation.

5. Attention is called to 3,5,3' triiodothyronine in thyroid hormone action. Triiodothyronine exhibits perhaps greater hormonal activity than thyroxine and can be shown to be derived from thyroxine in the extrathyroidal tissues. It has not been definitely established whether hormonal activity is shown by thyroxine itself or whether its entire effect is due to its conversion into triiodothyronine. Both substances are present simultaneously in the circulation and tissues (Gross and Pitt Rivers).[33]

Although all the answers are not known, modern investigators are attempting to unravel the physiological conundrum of hyperthyroidism. Each year witnesses the unveiling of newer knowledge which brings the physician and surgeon closer to the solution of thyroid diseases.

3

The Clinical Picture of Hyperthyroidism

PRIMARY HYPERTHYROIDISM is a term employed to designate toxic goiter also often called Graves disease Basedow s disease Flajani s disease or diffuse toxic goiter Hyperthyroidism may also result from adenomatous colloid goiter or cancer in the thyroid gland In these instances it is proper to employ the term secondary hyperthyroidism e g adenomatous goiter with secondary hyperthyroidism A patient having any one of these types of hyperthyroidism (usually a female patient since hyperthyroidism occurs much more frequently in women than men) may present herself to the doctor either because of toxic symptoms or because she has noted a mass in her neck The classical symptoms of thyroid toxicity are reviewed under figure 4

One of the significant aspects of hyperthyroidism is that it is a manifestation of a constitutional disorder Hence the dictum once a hyperthyroid patient always a hyperthyroid patient The thyroid enlargement itself is merely an outward sign of a hidden underlying constitutional disturbance with many ramifications

Thyroid enlargement is not of itself a serious or a death producing situation It is true however that it may be disfiguring and makes the individual self conscious because of a mass in the neck Thyroid enlargement in advanced cases of goiter does produce tracheal compression or discomfort due to pressure in the neck This so disturbs the patient that she may demand an operation for relief of pressure symptoms These local signs and visible distress are insignificant when compared to the systemic disturbed physiology underlying hyperthyroidism In figure 4 the various organs affected by excessive thyroid function are graphically illustrated

It is proper therefore to define primary hyperthyroidism as a widespread complex constitutional disorder (endocrinopathy) involving the thyroid other endocrine glands the tissues of the orbit the spleen the thymus the lymphatic reticuloendothelial hemopoietic muscular nervous and almost all other systems in the human body The cause for these underlying disturbances is not fully understood so that the exact etiological cause of primary hyperthyroidism has not been definitely established

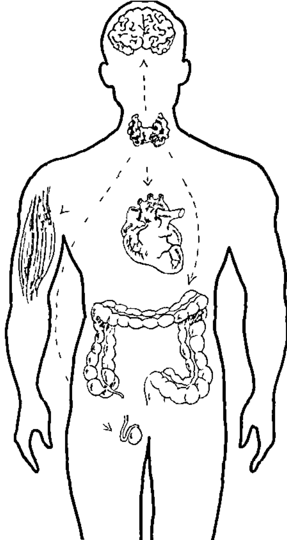


FIG 4 Spheres of influence attributed to the thyroid gland In addition to its metabolic function the thyroid gland takes an active part in maintaining the normal conditional balance of the neuromuscular circulatory digestive and reproductive systems This function is made manifest on these systems from the clinical picture resulting *from the extremes of hypofunction (myxedema) and hyperfunction (hyperthyroidism)* of the thyroid gland

Typical of myxedema are flabby hypotonic muscle sluggish circulation bradycardia menstrual disorders and sterility dry coarse skin and constipation In hyperthyroidism the muscular changes range from mild myasthenia to severe atrophy Tachycardia is common amenorrhea or oligomenorrhea is frequent Like the diminished intestinal peristalsis of myxedema the profuse sweating of hyperthyroidism is probably due in part to the action of the thyroid on the vegetative nervous system The effect on the central nervous system is even more pronounced and remarkable The thyroid hormone shortens the reaction time of the nerves and heightens their irritability Extreme toxic hyperthyroidism is characterized by emotional instability hyperexcitable nervousness tremor crying without cause and confused thinking The personality itself may undergo many changes Fatigability or rapid tiring is a characteristic symptom of hyperthyroidism Physical endurance and stamina are markedly reduced in the patient with excessive thyroid function (Adapted from an

Signs and Symptoms of Hyperthyroidism

As has been stated toxic goiter (thyrotoxicosis) means a symptom complex which not only produces thyroid enlargement but results in palpitation rapid pulse tremor irritability crying without cause and associated loss of weight (emaciation) due to an increased rate of nitrogenous and gaseous metabolism The above symptoms may be listed as classical expressions of excessive or hyperthyroid activity

There are two forms of toxic goiter namely primary and secondary In the primary type toxic signs and symptoms associated with a simultaneous enlargement of the thyroid seem to occur in an individual with a previously healthy thyroid gland It is usually of sudden onset with

TABLE 1 *Thyrotoxicosis Primary and Secondary Toxic Goiter*

Primary Thyrotoxicosis	Secondary Thyrotoxicosis
Affects a previously healthy gland	Affects previous goiter bearers only
Onset sudden and progress rapid	Onset gradual and course chronic
Exophthalmos common and often severe	Exophthalmos rare and usually slight
Nervous phenomena prominent	Nervous phenomena slight or absent
Basal metabolic rate very high	Basal metabolic rate moderately high
Cardiac symptoms may be inconspicuous until later stages	Cardiac symptoms prominent early marked auricular fibrillation
Goiter diffusely hyperplastic firm and small	Goiter usually nodular and large
Response to iodine medication often dramatic	Iodine medication often beneficial but less striking in effect

rapid progression and quite often is associated with protrusion of the eyes (exophthalmos) hence the term exophthalmic goiter (Graves disease or Parry s disease)

The secondary type of hyperthyroidism usually arises in patients in whom simple goiter (sometimes called parenchymatous colloid or nodular goiter) has existed previously for some time usually one or more years The onset of this type of hyperthyroidism is rather insidious and protrusion of the eyes is uncommon When exophthalmos does occur it is usually not very marked

From an etiological point of view there does not appear to be any relationship between the toxic goiters and the simple goiters The toxic types are not associated with environmental iodine deficiency As far as our knowledge enlightens us at the present time it does not appear that their distribution has any relationship to the geographical occurrence of endemic goiter In toxic goiters there is no doubt however that a derange

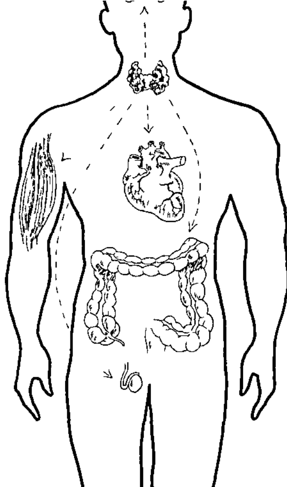


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shock illness or infection It is not an unusual story in the case history of an individual with exophthalmic goiter, to have the patient definitely equate the onset of symptoms with a shocking experience—for example the sudden death of a parent or relative a motor accident financial tragedy divorce or marital disturbance Other patients may present a history of a prolonged emotional anxiety such as studying for examinations or preparing for the legal medical or engineering professions Some thyroid patients will definitely establish the time of thyrotoxic symptoms with an attack of a virus infection a common cold or similar infective process

What actually happens within the thyroid gland due to these emotional or infective processes is of much theoretical speculation It can be stated however that the thyroid gland under the stress and strains previously mentioned has an exaggerated and uncontrolled secretory activity It continuously eliminates the thyroid hormone in large quantities so far in excess of what the human body requires that all the toxic symptoms of hyperthyroidism result This excessive elimination of thyroid hormone was called thyroid diarrhea by Kocher[146] The chemical alterations and the histological changes which take place in the gland of exophthalmic goiter (Graves disease) are most satisfactorily discussed by Harington in his classical textbook on the thyroid gland mentioned under physiology[8]

It is an established fact that insufficient supplies of iodine cause certain changes in the thyroid gland These changes result in goiter Characteristic glandular changes in goiter may be recognized under the microscope To fully understand the architectural alteration in the thyroid gland the histological structure of the thyroid should be known

The first thyroid alteration is due to iodine insufficiency and can be seen (under the microscope) in the epithelial cells lining the acinus These cells change from a flat or low cuboidal form to long columns High columnar epithelium is never seen in a normal thyroid gland In association with this hypertrophy of cells is a marked drop in the iodine content of the gland itself This is demonstrated by the diminution in the amount of colloid which absorbs the stain This colloid becomes rarified and filled with vacuoles Associated with this is an increased vascularity Microscopically this is demonstrated by tortuous engourged and congested blood vessels In addition the microscope reveals the formation of new vesicles within the connective tissue With the prolonged deprivation of iodine the thyroid gland will show hyperplasia characterized by an excessive multiplication of the cells comprising the follicular epithelium In addition there is a disappearance of the colloid fluid which becomes more marked as the hyperplastic process advances When the hyperplastic process becomes intense the epithelial lining folds over itself so that it may even fill

ment of iodine metabolism does exist It must also be remembered that there would be no secondary toxic hyperthyroid patients if the e individuals did not have simple non toxic goiters to start with

Exophthalmic Goiter (Primary Hyperthyroidism, Graves Disease)

The first case of exophthalmic goiter was recorded in medical literature by Caleb Hillier Parry (1755–1822) [146, 9] His description of this disease was 'There is one malady which I have in 5 cases seen coincident with what appeared to be enlargement of the heart, and which so far as I know has not been noticed in that connection by medical writers The malady to which I allude is enlargement of the thyroid gland ' Parry observation was made in 1786 and all students of medical history agree that if anyone s name deserves to be attached to the disease it should be Parry s However this syndrome has been known as Graves di ease in England and the United States and as Basedow s disease in continental Europe The use of these proper names still persists in spite of the fact that Graves description was less accurate than Parry's and was made much later (in 1835 to be exact) Dr Basedow s presentation of this disea e, although it was more complete did not appear until 1840 [146] In Italy primary hyperthyroidism is called Flajani s disease in honor of an Italian physician who described the disease in 1800 [146]

Etiology of Hyperthyroidism

Under the discussion of thyroid physiology several facts were presented which intimated that etiological agents when acting in a disturbed fashion may result in hyperthyroidism The exact mechanism cannot be stated and proven didactically However clinical experience and laboratory experimentation have brought forth certain aspects of this disease which should be considered in its etiology For example clinical studies definitely establish that exophthalmic goiter is much more common in women than in men that fair haired and fair complexioned women fall victims to this disease more than dark haired and dark complexioned women Exophthalmic goiter is not commonly seen before 15 and is infrequently encountered after 50 years of age It seems to be much more frequent in per ons who do mental work than in those who do manual labor Exophthalmic goiter produces in women an artificial vivacity and temperament which label some of them the life of the party

In the etiology of this disease one may also state that some patients undoubtedly have inherited a nervous mechani m *which is not very stable* and which may predispose them to hyperthyroidism In such individuals however the immediate cause for the di ease may be a serious emotional

plasia it does not return to an exact anatomic normal state Because of these changes the colloid goiter is the nearest approximation to the normal both from an anatomic and physiochemical point of view Functionally the colloid gland is able to perform all the reactions which are exhibited by a normal thyroid gland David Marine of Montefiore Hospital New York has shown that the hyperplastic process subsequent to iodine deficiency may develop from a colloid gland basis in exactly the same way as it does in a normal thyroid gland[163] Thus the resting goiter (colloid gland) will again go through the same cycle of changes whenever the iodine deficiency which originally caused the colloid goiter is renewed

In summary therefore it may be stated that the developmental stage of a primary hyperplasia that is one arising on a normal gland basis is marked by a drop in the iodine store a decrease in colloid substance proliferation of the epithelial cells which change from low cuboidal to columnar and a larger and softer gland In the involutionary or physiological recovery stage which may occur spontaneously or may be hastened by iodine administration and is the usual mode of termination of an active hyperplasia the gland becomes firmer a greater amount of denser and intensely staining colloid accumulates in the follicles high columnar epithelium returns to the normal columnar type and there is an increase in the iodine store Atrophy or the state of physiological exhaustion is less common but is seen in the myxedema of children and following acute hyperplasias of young adults Here the colloid is very markedly reduced or absent and the follicles are obliterated by cell death The stages of a secondary hyperplasia that is one developing on a colloid gland basis are not essentially different from those arising in a normal gland

Colloidophagy in the Thyroid Gland

In 1940 Japanese investigators were among the first to call attention to the fact that the colloid of the normal thyroid gland contained certain cells which had the appearance of monocytes[165] Three years later colloidophagy in chronic thyroiditis was described by Buno[166]

Prior to this time Loeb and Basset mentioned macrophages in the thyroid follicles of animals[164] They believed that colloid resorption by phagocytes plays a significant part in the normal removal of colloid After injection of thyrotropic hormone in lizards Eggert saw wandering cells enter the hyperactive follicles ingest colloid and carry it into blood vessels[164] Williams implanted transparent chambered thyroid tissue into rabbit ears and observed in the living tissue macrophages entering follicle Thyrotropic hormone increased the activity of these colloidophages There was no evidence of degeneration of the epithelial wall of the invaded follicles[164] Williams believed that some special chemical alteration of the colloid stim

the acinus space excluding colloid completely As a result the entire gland may eventually become a solid mass of functionless cellular tissue With the progression of hypertrophy and hyperplasia the gland becomes more visibly enlarged If it becomes truly extensive, the abnormal development becomes quite visible in the neck

If the iodine deficiency which has stimulated the hyperplasia becomes so severe that the degenerative process continues, then the thyroid gland,

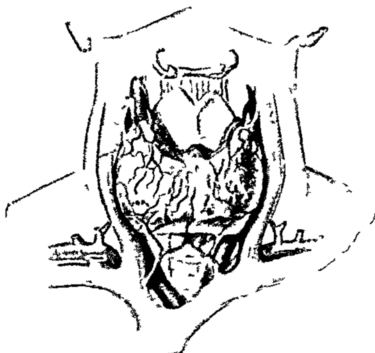


FIG 5 Anatomy of diffuse toxic goiter (primary hyperthyroidism or Graves disease) (Reprinted from Pfizer *Spectrum* appearing in the J A M A)

not able to meet this stress and strain will eventually become completely exhausted and atrophied Such a state may be associated with myxedema Conversely, the iodine deficiency may be temporary and the thyroid gland may be able to tolerate the transient deprivation until iodine is administered again or until the physiological stimulus which has resulted in the unusual demands on the thyroid has been eliminated When this occurs and the stimulus is removed the excessive secretory activity ceases the hyperplasia no longer takes place and involution occurs with the thyroid gland returning to a quiescent phase

It is well to recall that once the thyroid gland has undergone hyper

from the pituitary gland The stimulated cells react by producing t metabolism activating thyroid hormone This hormone normally inhib overproduction of thyrotropin by means of a delicately sensitive autoc balancing mechanism By means of histological section acinar measu ments can be determined which categorize the type of epithelial alterati into the six progressive phases of the toxic thyroid gland

1 Epithelial hyperplasia
2 Lympho epithelial hyperplasia
3 Focal lymphoid hyperplasia
4 Diffuse lymphoid hyperplasia
5 Fibrolymphoid hyperplasia
6 Fibrosis

The degree of toxicity is usually divided into three parts namely mi moderate and severe

According to Levitt most of the patients studied varied between mo erate and severe degree of toxicity in the epithelial hyperplasia pha The lympho epithelial hyperplasia phase showed a mild degree of toxic in 24 per cent and severe toxicity in 30 per cent of the patients studied

In focal lymphoid hyperplasia the incidence of mild toxicity was per cent moderate toxicity was 36 per cent and severe toxicity was fou in 28 per cent of the patients studied Diffuse lymphoid hyperpla patients generally displayed mild and moderate toxicity similar to t focal lymphoid group with severe toxicity falling to 21 per cent

Fibrolymphoid hyperplasia (Hashimoto s disease) patients showed m toxicity in 60 per cent and moderate toxicity in 33 per cent of patien The fibrosis (Riedel s struma) was found in patients over 40 years of a None had any specific history of any preceding severe thyrotoxicosi

Methods for Determining Thyroid Function

Many physicians and surgeons have overemphasized the basal metabo rate as a criterion for arriving at a diagnosis of hyperthyroidism Thyr surgeons have learned to rely on the pulse rate and its stabilization und *treatment as a more reliable criterion for toxicity and operability* A elevated pulse which has fallen and has been maintained at a plate level indicates a satisfactory response to therapy and suggests to t surgeon that thyroidectomy may be performed This is true even if t basal metabolic rate remains elevated Faulty recordings of the ba metabolic rate may result from technical inaccuracies and the failure secure the patient full cooperation Therefore this method of evaluati should not be relied upon entirely

ulates the entry *of macrophages into thyroid follicle but did not* suggest the nature of this chemotactic substance. Several observations suggest that thyrotropic hormone increases the content of the thyroid in phospholipid. Morton and Schwartz demonstrated in vitro that phospholipid is increased markedly in supravital thyroid tissue after adding thyrotropin.[16] Dobyns found a large number of lipid droplets in the thyroid epithelium of guinea pigs after injection of thyrotropin (Antuitrin T). Ferguson injected subcutaneously lipid extracts from thyroid colloid into guinea pigs and saw histiocytes, giant cells and lymphocytes attracted by the injected lipid.[167] In the colloid and interfollicular tissue of positive cases macrophages were found with granules that stained black with sudan black B.[164, 165, 166, 16]

In 16.2 per cent of thyroids obtained by autopsy, macrophages were found in the lumen of follicles. The involved follicles were surrounded by lymphocytes. There was no relationship between the presence of colloidophages and cause of death. Women 50 years or older predominated in positive cases.[16] In 49 of 75 surgical goiters colloidophages were noticed. They were present not only within the follicle lumen but also in the follicle wall, the center of lymph follicles and in the interfollicular tissue. Exophthalmic goiters and thyroids with chronic thyroiditis were most frequently represented in positive findings.[164] This new study of the cytology of the thyroid gland may be of future value in studying thyroid activity and neoplastic diseases of the gland.

Thyroid Disturbances in Terms of the Matrical Theory

DeCourcy of Ohio has brought attention to the matrical theory as applied to the thyroid gland.[345, 491] The matrical theory was presented first to explain the origin of cancer as a disease of the matrix. Its application to the thyroid gland brings forth the hope that a new interpretation may be used to evaluate the mysteries of the diseases of this gland. It may therefore become evident that the concept of a transcendent dynamically *integrated matrix may be used to construct the basis for an entire new* concept in the disturbed human physiopathology. The exact status of the matrical theory in thyroid disease cannot be evaluated at the present time. However, future studies may bring light on the development of certain thyroid diseases. The specific diseases in question are arteriosclerosis of the thyroid as well as benign and malignant tumors of this gland.

T. Levitt of London in his masterfully composed textbook postulates six progressive phases of the toxic *thyroid gland.*[34] *His postulates* are based upon the alteration of epithelial tissue. He believes, as do many others, that the epithelial cell is the true center of thyroid function. It is this basic cell which is altered due to the thyrotropic hormone arising

tests shows that the basal metabolism test is of limited value in the diagnosis of thyroid function.[344]

A New and Simple Test for Hyperthyroidism Employing L-Triiodothyronine and the 24 Hour I^{131} Uptake Method

The administration of thyroid, thyroxine or triiodothyronine causes a sharp reduction in I^{131} uptake by the thyroid in euthyroid subjects but little if any change in Graves' disease. This distinction is so clear cut that an investigation was undertaken by Werner and Spooner to establish whether the reaction would be as useful diagnostically as theoretic results implied. Since thyroid contains iodides and several organic iodinated compounds which might induce false positive results and since the effects of thyroid and of thyroxine are protracted after treatment is discontinued, crystalline triiodothyronine was chosen as the test agent. The material is available in pure form and has a more rapid half life within the body than thyroxine. While this study was being pursued Greer independently was investigating the use of thyroid for the same purpose and obtained similar results as Werner and Spooner.[0]

Summary of this Test for Hyperthyroidism

1 Triiodothyronine 75 or 150 μg daily by mouth for 8 days caused a sharp decrease in the twenty four hour I^{131} uptake in 48 euthyroid patients without thyroid disease so that no value exceeded 20 per cent. In contrast no value under 35 per cent was obtained in patients with toxic goiter following triiodothyronine administration. Side effects occurred in euthyroid patients only with a dosage of 150 μg and were relatively minor.

2 About a third of the euthyroid patients in this series had initial 24 hour I^{131} uptake values in excess of 40 per cent and a third of the hyperthyroid patients had uptakes less than 55 per cent. Triiodothyronine was virtually specific in clarifying the diagnosis in this group with overlapping values.

3 Triiodothyronine was valuable in establishing the activity of the eye complications of Graves' disease. Euthyroid patients with the early eye signs of Graves' disease and patients with overt hyperthyroidism showed an abnormal response to triiodothyronine but patients in sustained remission reacted normally.

4 Patients with nontoxic diffuse goiter responded like normal subjects to the administration of triiodothyronine whereas 5 of the 21 patients studied with nontoxic nodular goiter had no response to triiodothyronine administration even though the initial uptake values were within the

In addition to the indirect calorimetry or oxygen consumption test other methods are used in the evaluation of the patient with thyroid disease These are

1 Serum cholesterol level
2 Radioactive iodine uptake
3 Blood protein bound iodine level
4 The McWhirter Freibrun metabolic calculator

The latter method is a device that utilizes available information (e g body weight blood pressure and pulse rate) from which the basal metabolic rate is determined by a standard formula Of these various methods only oxygen consumption, serum cholesterol determination and the use of the metabolic calculator are suitable for the doctor in his office [160]

The measurement of the concentration of radioiodine (I^{131}) in the thyroid gland and the chemical determination of the protein bound iodine of the blood serum are laboratory tests that have gained increasing use in the diagnosis of thyroid disease A brief comparison between these methods namely radioiodine and protein bound iodine determination and the contrast of these tests with the determination of the basal metabolic rate is made here By means of the Geiger counter the concentration of the radioiodine in the thyroid gland is measured one hour and 24 hours after the oral administration of 10 μc of I^{131} The patient is in a fasting state to facilitate the one hour determinations of radioiodine A careful history of any previous intake of thyroid extract iodine medication iodized salt or iodized oils as used in x ray diagnosis is obtained to rule out any errors from these sources Six cubic centimeters of blood are drawn into a tube and the protein bound iodine is determined by the method of Brown This method enables the technician to make up to 12 duplicate determinations daily The same iodine compounds which interfere with the I^{131} tests adversely affect the determination of protein bound iodine The I^{131} and protein bound iodine tests performed in 50 euthyroid and in 25 hyperthyroid patients revealed that in normal patients more than 97 per cent of the results were between the limits of 5 per cent and 45 per cent I^{131} concentration One hundred per cent were between 3 5 and 8 protein bound iodine gamma per 100 cc of serum In the hyperthyroid patients I^{131} concentration was between 50 per cent and 85 per cent in over 94 per cent of the patients studied In all cases the protein bound iodine per 100 cc of serum was between 8 and 16 or more Despite the expected overlap between the higher normal and lower hyperthyroid readings there was a clear cut separation between the euthyroid and hyperthyroid group with both tests This comparison of thyroid function

tions Found among children only in districts where goiter has been severely and continuously endemic for long period of time In contrast to sporadic cretinism the endemic type exhibits a wide range of physical and mental defects with many mixed and intermediate varieties Is notably associated with deaf mutism and cardiac failure Subcutaneous swellings seen in sporadic cretinism are often absent	reach a large size Histologically the follicles are greatly distended and rich in colloid The percentage iodine content is less than normal but owing to increased size the total may be equal to or greater than normal 3 Nodular Goiter (Struma Nodosa) Commonest form in patients over age of 30 in all endemic areas Is the result of long continued action of the goiter producing *factor working perhaps* through generations and intensified by in breeding Gland composed of nodular masses (either of parenchymatous or colloid structure) embedded in a dense overgrowth of tough fibrous connective tissue The nodules may be generalized or localized thus (a) Generalized Multiple Synonyms Adeno parenchymatous Goiter Adenomatosis Multiple Adenomata Bosselated Goiter (b) Localized Single Colloid Adenoma Parenchymatous or Foetal Adenoma of Wolfler Non Parasitic Cysts	Affects previous goiter bearers only hence secondary Onset gradual and course of disease chronic Exophthalmos rare and usually slight Nervous phenomena slight or absent Basal metabolic rate reaches + 30 per cent Goiter usually nodular and large exception may be diffusely paren*chymatous or colloid in type* Iodine medication often beneficial but not so striking in effect as in primary thyrotoxicosis

TABLE 2 *Classification of Thyroid Disturbances*

Thyroid Function Diminished or Absent Hypothyroidism	No Obvious Signs of Abnormal Bodily Function Sometimes called Euthyroidism	Excessive Thyroid Function Hyperthyroidism
Myxedema—Atrophy of Thyroid Myxedema, the classical manifestation of hypothyroidism, is characterized by lassitude, inertia, mental torpor, depression, headaches, obesity, constipation. Since the thyroid is atrophied, the condition is non-goitrous. It occurs in both adults and children.	*Simple Goiter*—Endemic, Sporadic A hypertrophy of the thyroid gland caused by increased need of thyroid secretion. The condition is one of thyroid enlargement only, and is unaccompanied by any definite clinical symptoms except perhaps a *feeling of tiredness*. Hence the term simple or benign goiter. The state includes:	*Thyrotoxicosis* or *Toxic Goiter* Thyrotoxicosis is the classical manifestation of hyperthyroidism. It is characterized by nervousness, tremor, emaciation, irritability, *tachycardia, sweating*. Is of two distinct types, viz:
1 Adults (Gull's Disease) The term Myxedema is usually reserved for the adult form (also known as Gull's Disease), that in children being named Sporadic Cretinism.	Transitory Reversible Types 1 Physiological Enlargement Includes the temporary enlargements of puberty and pregnancy due to increased demands on the thyroid at these times. Normally, adolescent enlargements, which are soft, smooth and symmetrical, disappear spontaneously. If however the iodine deficiency persists they may develop into forms of established goiter, viz:	1 Primary Thyrotoxicosis *Synonyms*: Exophthalmic Goiter, Parry's Disease, Graves' Disease, Basedow's Disease, Flajani's Disease. Affects a previously healthy gland, hence primary. Onset sudden and progress rapid. Exophthalmos common and often severe. Nervous phenomena prominent. Basal metabolic rate very high (may be > +100 per cent). Gland smooth, firm, diffusely hyperplastic and symmetrical, colloid and iodine poor, not very big but always enlarged a little. Response to iodine medication often dramatic.
2 Children (Sporadic Cretinism) Associated with atrophy of the thyroid, hence non-goitrous. Usually congenital. Sporadic cretins rarely born of goitrous parents. Exhibit markedly *uniform* physical and mental characteristics. Are lethargic, dull, of sub-normal temperature, round head, coarse pasty face, short and scanty hair and skin thickened by subcutaneous gelatinous deposits. Rarely survive to adult life.	Established Irreversible Type 1 Parenchymatous Goiter (Struma Diffusa Parenchymatosa) Occurs commonly in children in areas of high endemicity (e g Switzerland), seldom seen after puberty. The goiter is diffuse, symmetrical, firm and of small size. Histologically there is extensive hyperplasia, greatly *increased number of follicles* but devoid of colloid. Iodine content always reduced both in percentage and total.	2 Secondary Thyrotoxicosis Synonyms: Toxic Non-Exophthalmic Goiter, Toxic Adenoma of the Thyroid, Adenoma with Hyperthyroidism, Hyperfunctioning Adenomatous Goiter, Secondary Basedow, Basedowified Goiter.
Endemic Cretinism—Goitrous Sometimes termed Cretinic Degeneration. Always associated with goiter. Is the consequence of thyroid deficiency acting over many genera	2 Colloid Goiter (Struma Diffusa Colloides) Is the common type in areas of low endemicity (e g England and Wales), develops usually at or near puberty and is rare in typical form after age of 30. The goiter is diffuse, symmetrical, rather soft, and may	

neck lesions are metastases from either primary or secondary pulmonary cancers

Aspiration of a neck mass has been thought on many occasions to be either a means of biopsy study or for the purpose of injecting an iodized substance for x ray study The procedure of aspiration is not recommended for neck masses

By utilizing the cardinal procedures of inspection palpation and auscultation valuable information becomes readily available The first revelation is whether the pathology is one mass or multiple masses If the mass trans



FIG 6 Anterior view of a branchial cyst located in the upper carotid triangle of the neck (Eisendrath Surgical Diagnosis Philadelphia W B Saunders Co 1907)

illuminates a cystic tumor must be considered Compression of the mass suggests its consistency For example vascular masses are compressible and esophageal diverticula empty with compression Deglutition produces motion in masses of thyroid origin When the tongue protrudes motion in a neck mass indicates a thyroglossal cyst or fistula (attachment to the base of the tongue) The presence of pulsations may be deceiving for an underlying artery may transmit pulsations A mass that is immobile from its incipiency strongly suggests an inflammatory lesion Fixation of malignant tumors occurs only when the malignancy has infiltrated A well defined tumor edge that is smooth suggests a benign lesion Injury to the neck area followed by a rapidly developing mass indicates hemorrhage Tenderness and heat over the mass suggest inflammatory lesions

The rate at which a mass may change in size may offer a clue to the etiology of the mass

normal range Radioautographs of three of these glands revealed the nodules to be functionally active

From the results obtained it appears that a new diagnostic method has been added to the armamentarium of the thyroid diagnostician

Recognition of Neck Masses

When presented with a mass or nodule in the neck thought must also be given to other causes for a tumor in the neck As a general statement it may be stated that tumors in the midline of the neck are usually of thyroid origin

In order to institute proper therapy any mass in the neck must be identified whenever possible A mass or masses in the cervical region usually can be evaluated and identified Exceptions occur in which even the most sagacious examiner may err However by means of a careful history physical examination, x ray and biopsy studies a satisfactory diagnosis can be made A proper diagnosis enables the surgeon to decide whether the lesion is amenable to surgical removal or is a result of medical enlargement of lymph nodes or other medical diseases

As is the procedure of examination in other regions of the body so it is in the cervical area that one pursues the classical method of inspection, palpation auscultation and laboratory studies

The procedure of inspection assists in localizing the lesion Location is quite helpful in diagnosis because of the anatomy and embryology of the structures found in the neck For example a midline neck mass is usually thyroid in origin and rarely a dermoid cyst A lateral mass anterior to the border of the sternomastoid muscle would indicate a branchial cyst or fistula Inspection reveals the response of the tumor to motion The thyroid masses move upward with deglutition as do masses of thyroglossal origin when the tongue is protruded

Palpation assists in confirming the location of the mass In addition it gives valuable information as to size shape and consistency movability and the presence or absence of pulsations In the course of palpation the insertion of a finger into the depths of the oral cavity may reveal valuable information This simple procedure differentiates neck masses from those arising from the floor of the mouth

The use of the stethoscope is an aid in auscultation The bruit over vascular lesions as an arteriovenous fistula or aneurysm may be discerned via auscultation A bruit is often heard over the thyroid gland in primary hyperthyroidism

Roentgenograms are not taken often enough in the course of study for neck pathology The x ray should include study of the chest for many

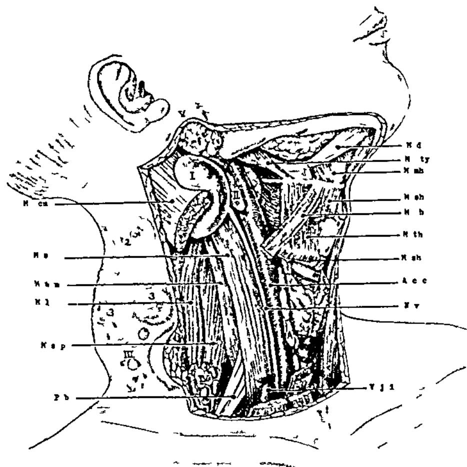


Fig 8 Location of neck masses in lateral and posterior aspect

Key

A Metastatic thyroid cancer

1 Fatty tumor *2* Sebaceous cyst *3* Infection carbuncle

I Branchial cyst *II* Carotid body tumor *III* Neurofibroma *IV* Hygroma V Parotid tumor

M cm M sternocleidomastoideus *M s a* M scalenus anterior *M s m* M scalenus medius *M l s* M levator scapulae *M s p* M scalenus posterior *P b* Plexus brachialis *M d* M digastricus *M sty* M stylohyoideus *M mh* M mylohyoideus *M sh* M sternohyoideus *M oh* M omohyoideus *M th* M thyreohyoideus *A c c* A carotis communis *N v* N vagus *V j i* V jugularis interna

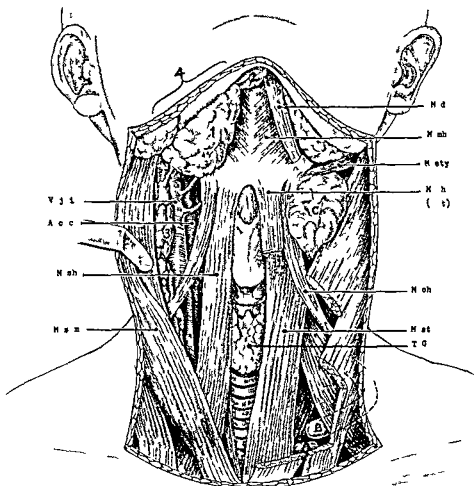


Fig 7 Location of masses in anterior aspect of neck

Key

A Virchow's node *B* Cervical rib *C* Teratoma

1 Enlarged submaxillary gland due to obstruction of duct calculus or tumor *2* Sublingual gland enlargement *3* Lymphadenopathy *4* Mikulicz disease

V j i V jugularis interna *A.c.c* A carotis communis *M.sh* M sternohyoideus *M.scm* M sternocleidomastoideus *M d* M digastricus *M mh* M mylohyoideus *M sty* M stylohyoideus *M oh* M omohyoideus *M st* M sternothyreoideus *T G* Thyroid gland

Rapid enlargement (after meals)	indicate	Esophageal Diverticulum
Accelerated Progression (hours or days)	indicates →	Acute Inflammation or hemorrhage
Slow development (weeks or months)	indicate	Chronic Inflammation (tuberculosis or neoplasia)

With a preliminary or tentative diagnosis available the examiner should then institute a mental differential diagnosis By means of a simple classification many diseases can be eliminated and a mass or masses in a neck identified (cf Chart and Figures 7 and 8)

In general pathologic enlargements in the neck are due either to medical or surgical diseases The medical diseases are inflammatory processes of the salivary gland lymphoma and similar entities Surgical lesions are those of thyroid origin pathologic processes finding their origin in embryological disturbances or tumors either benign or malignant By the process of elimination the diagnosis of tumor masses can be confined to a small number and then identified The decision as to surgical intervention can be determined with adequate identification

At this point one may well describe the characteristics of the thyroid gland on physical examination The gland is hard (after iodinization especially) and the superior poles come to a blunt point (similar to a tent) When nodules are present the gland may harbor cancer mutiple adenomata or hyperparathyroid tumor In order to palpate the gland adequately the examiner should stand in front of the patient and turn the patient s head toward the side to be examined This will relax the sternocleidomastoid muscle The examiner uses one hand to push the larynx toward the side to be examined With the other hand the thumb is pressed anterior to the sternocleidomastoid muscle and the second and third fingers are placed posterior to this muscle The patient is then instructed to swallow In so doing the gland may be adequately palpated In this way the length and breadth of the thyroid shield the isthmus and the superior and inferior poles can be examined Thus the shape size and consistency of the gland can be evaluated When the lower pole is not felt a roentgenogram of the trachea is indicated in order to determine tracheal deviation substernal and/or subclavicular extension

The classification charts on pages 36 and 38 although not complete will be an aid in differentiating the most commonly seen simple neck tumors

Classification of Neck Tumours as to Location

MEDIAN

1. Undescended Thyroid
2. Thyroglossal cyst
3. Pyramidal thyroid lobe
4. Adenoma Thyroid Isthmus
5. Other Thyroid Pathology
6. Dermoid Cyst
7. Infrahyoid Bursa

SUBMAXILLARY

1. Enlarged submaxillary salivary gland due to obstruction of duct (calculus) or tumour
2. Sublingual gland enlargement
3. Lymphadenopathy
4. Mikulicz's Disease

LATERAL

Single Mass

1. Branchial cyst
2. Carotid Body tumour
3. Aneurysm
4. Neurofibroma
5. Hygroma
6. Tuberculous Abscess
7. Esophageal Diverticulum
8. Laryngocele
9. Parotid tumour [illegible]
10. Parathyroid tumours
11. Actinomycosis

Multiple Masses

1. Metastatic Thyroid Cancer
2. Tuberculous Adenitis
3. Metastatic Carcinoma
   a. Primary
   b. Secondary
4. Lymphadenopathy
   a. Hodgkin's Disease
   b. Lymphosarcoma
   c. Boeck's sarcoid
   d. Glandular Fever

POSTERIOR

1. Fatty tumours
2. Dermoid cyst
3. Sebaceous cysts
4. Infections (carbuncle)
5. Meningocele

SUPRACLAVICULAR

1. Virchow's Node
2. Lymphadenopathy
3. Teratoma
4. Pancoast tumor
5. Cervical Rib

See Figs. 7-18

may be seen on the map on page 44 (Fig 13) The black area on this map are for the most part mountainous regions or old glacial areas In terrain of this type most of the iodine has been washed out and carried via the rivers into the sea A very low concentration of environmental iodine is characteristic of all these countries Herein lies the cause of endemic goiter Endemic goiter is the response on the part of the thyroid gland to the iodine deficiency Therefore the prevention of endemic goiter

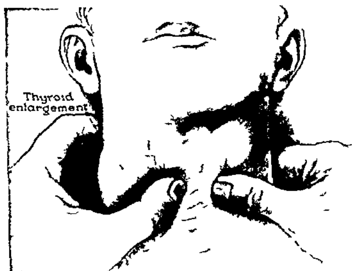
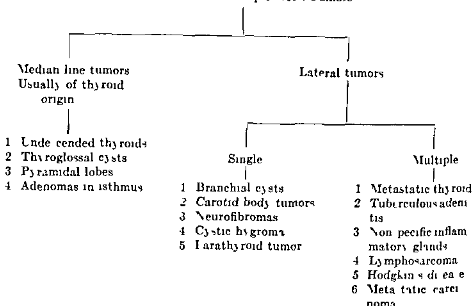


FIG 9 A method of examining the thyroid gland The trachea and larynx are displaced toward the side to be examined The index finger and the other fingers are placed behind the sternocleidomastoid muscle and the thumb is placed anterior to the muscle The patient is then asked to swallow and in this fashion the thyroid gland can be palpated satisfactorily Each lobe of the thyroid should be palpated separately In addition to size shape and consistency each lobe is carefully examined for the presence of nodules (Courtesy of the Mayo Clinic Pemberton J and Black B M Cancer of the Thyroid Am Cancer Soc 1954)

from a physiological point of view revolves about a substitution of artificial iodine for the natural iodine deficiency Artificial iodination over a period of years will in the course of time insure a goiter free community Those patients in whom endemic goiter has developed naturally will not respond to the administration of iodine That is to say iodine given to a patient with an existing endemic goiter will not dissolve that goiter The only method whereby a pre existing visible goiter can be removed is by means of the surgeon s scalpel

In a consideration of endemic goiter the most efficacious therapy is prophylaxis Various methods of administering iodine as a goiter prophy



On occasion the surgeon may examine a patient with toxic thyroid symptoms and not find anything of significance in the gland itself. However he may palpate one, two or more nodules along the anterior border of the sternocleidomastoid muscle. These nodules may be lymph nodes with metastatic thyroid tissue. At one time it was thought that these nodules were 'aberrant thyroid' tissue. *More recent study indicates that these* lesions are metastases arising from primary thyroid cancer.[91, 96] When the examiner encounters a patient as mentioned above, a study of the following table will enable him to differentiate metastatic thyroid nodules from other diseases producing nodules along the anterior border of the sternocleidomastoideus. (Cf. table 3, pages 40–41.)

Endemic Goiter

Within recent years there has been accepted into the lexicon of medicine a new word called geomedicine. Geomedicine is the study of the natural history of disease by means of comparing the clinical picture of certain illnesses in one locality with the clinical picture of the same disease as revealed in another geographical location. A classical example of the value of geomedicine is masterfully exemplified in the book entitled 'Endemic Goiter,' in which man's adaptation to iodine deficiency is studied.

Geomedicine has been of especial interest to the students of endemic goiter. There are various endemic goiter regions in the world. Their location

Metastatic thyroid tumors	Usually under 40	Single or multiple masses occurring in chains along sternomastoid muscle	Movable gland like masses	May be none	5 to 15 year arrest of disease with adequate treatment	Papillary cystadenoma or papillary adenocarcinoma

* This chart is taken from Aberrant Thyroid by Frank H. Lahey and Bernard J. Ficarra. Reproduced by permission of Surg Gynec & Obst 82 705-11 1946

TABLE 3 *Differential Diagnosis of Main Diseases Confused with Metastatic Tumors Arising in Thyroid Gland*

Disease	Age	Distribution of l	Character f m	A t d f nd gs	Course	Biopsy
Tuberculosis	Infants and children	Associated with general or local lymphadenopathy	Tender glands caseous matted together	Evidence of tuberculosis elsewhere occasionally	Chronic	Lymph node containing Langhans giant cells tubercles
Lymphosarcoma	Usually over 40	Main group of cervical glands involved	Large mass matted glands not tender	Debility picture of chronic illness	Usually fatal within 1 year	Lymph node with actively proliferating lymphoid cells in fine reticulum
Hodgkin's	Mainly young adults	Local glandular enlargement gradually becoming generalized	Massive discrete glands not tender	Fever (Pel Ebstein type) eosinophilia	Chronic with fatal outcome in 2 to 4 years	Lymph node with Reed Sternberg giant cells and eosinophils
Inflammatory glands	Any age	Regional glandular enlargement according to area infected	Enlarged tender glands	Evidence of primary infection fever leukocytosis	Rapid recovery with treatment	Hyperplasia of lymph node
Metastatic carcinoma	Usually elderly adults	Usually 1 or 2 prominent glands	Hard firm glands	Evidence of cancer in thyroid pharynx stomach or lung	Gradually downhill and fatal	Metastatic carcinoma

laxis has been tried The mo t sati factory method is iodized salt The quantity of iodine nece ary to add to table alt in order to prevent goiter is very minimal To be exact all that is needed is one part iodine to 100 000 parts of alt (1 100 000)

The anatomy of endemic goiter (adenomatous colloid goiter) is such that it is made chiefly of solid nodules and cy ts Both these cysts and nodules



Fig 12 Photograph taken in the Peruvian Andes showing a large endemic goiter This patient did not have respiratory distress and was not cyanotic Since the thyroid is so clo e to the trachea one might expect some tracheal compression and respiratory embarrassment This did not occur in this young man becau e the goiter is in a de pend nt position and external in front of the sternum This po ition in fact pulls the goiter away from the trachea rather than pre sing or occlu ding it (Courtesy of E A Sharp and F H Payne of Parke Davis & Co Detroit Michigan)

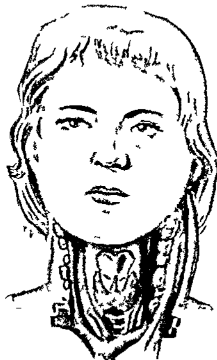


Fig 10 Anatomy of cervical lymphadenopathy (Reprinted from Pfizer *Spectrum* appearing in the J A M A)

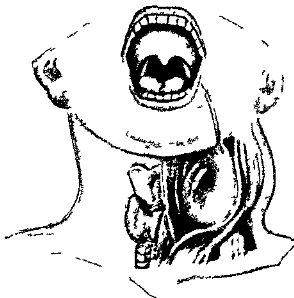


Fig 11 Anatomic location of branchiogenic cysts Cysts and fistulas of branchiogenic origin are usually found along the anterolateral side of the neck from the upra auricular region to the clavicle This is in contradistinction to cysts and fistulas of thyroglossal origin which are found in the midline (Reprinted from Pfizer *Spectrum* appearing in the J A M A)

vary in size from micro copic diameters up to tennis or golf ball size The olid nodules will be similar to the common types of benign thyroid adenomata It i rare to find malignant ti ue in this type of goiter The cysts themselves may contain material which in con istency may vary from thick jelly or chee e like material to clear fluid (degenerated cy ts with inactivated colloid) Variation in the appearance of the cysts from pale water color to dark brown or black (old hemorrhage) may be noted Some cyst are very thin walled and break during manipulation Coar e trabeculation with thick fibrous ti sue and cattered islands of parenchymatous ti ue are seen under the micro cope In addition micro copic tudy demon trates high columnar epithelium re embling the hyperpla tic thyroid ti ue of Graves di ea e This hyperplasia will be seen especially in tho e in tances of adenomatous colloid goiter with econdary hyperthyroidi m The epithelial lining of the large follicles and the cysts is of the quamou type

Calcium as a Goitrogenic Agent

In a geomedical tudy of the distribution of goiter thought must necessarily be given to calcium as a factor in the cau ation of goiter The calcium theory was put forth about one hundred years ago but wa not subjected to much thought or con ideration until more recent years when *geomedicine commenced to demon trate the importance of calcium* It appear that calcium may act as a goitrogenic agent although the preci e conditions of diet under which it exerci es its effect are not fully understood It i known that iodine can counteract the goitrogenic action of calcium in some in tances by preventing thyroid hyperplasia in others by e tablishing a colloid gland A field survey covering an area of 1 000 square miles performed in Calcutta India in 1835 led J McClelland to report his findings to the Medical and Physical Society of Calcutta He concluded that the cause of goiter in that locality was as ociated with limestone formations and was water borne According to him Goitre does not depend on temperature altitude or aspect of irregularities on the surface of the earth on hereditary taint nor on the usual causes of glandular enlargements in other parts of the body McClelland probably was the first to systematically attempt to correlate the geological features with the occurrence of goiter He brought attention to the fact that the damp calcareous *bhat* soil in the Gonda and Gandak valleys east of Gorakhpur are goitrou areas whereas the dry siliceous *bangar* soils in the Gogra valley to the south of same district are non goitrous

In 1931 Baumann and his as ociates publi hed in the *Journal of Biological Chemistry* results on thyroid deficiency caused by feeding rabbits with cabbage until a palpable goiter was produced They showed that these animals retained calcium magnesium and phosphorus The ad

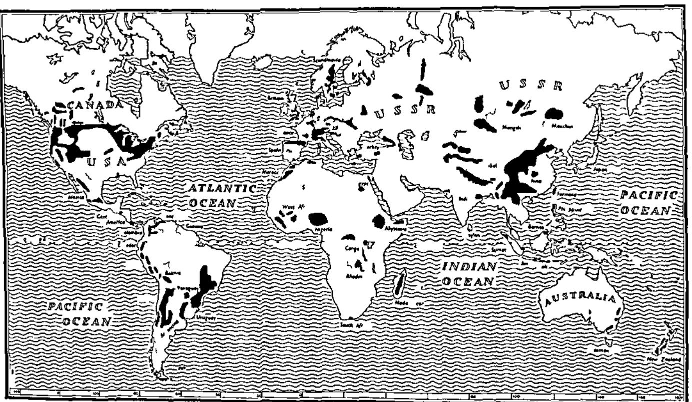


Fig 13 The goiter areas of the world (Chilean Iodine Educational Bureau London England)

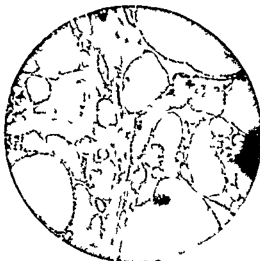


Fig 15 Microscopic picture of adenomatous colloid goiter The well filled colloid vesicles of varying sizes and shapes are prominent (Price L W Histology of the Thyroid Gland Medicine Illustrated Feb 1949)



Fig 16 Microscopic section of colloid adenoma (or adenomata) as seen in colloid goiter The presence of giant like colloid filled acini and the attenuated vesicular epithelium are characteristic of this entity (Price L W Histology of the Thyroid Gland Medicine Illustrated Feb 1949)

ministration of a small amount of iodine converts such thyroid to the normal colloid containing state and restores the balance of these elements by increasing the amount excreted These investigators believed that the retention of calcium is directly associated with the development of simple goiter

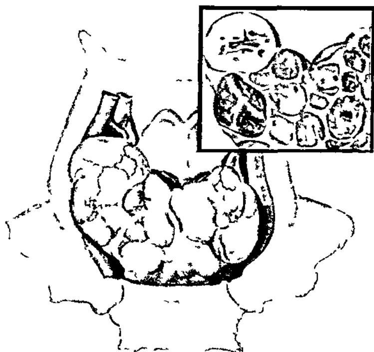


Fig 14 Anatomy of adenomatous colloid goiter also termed nontoxic nodular goiter Insert shows a fetal adenoma The structure of fetal adenoma presents the microscopic picture of numerous small alveoli lined by low cuboidal epithelium without colloid Another type of fetal adenoma contains small round cells with heavily stained nuclei In both types the periphery of the tumor is composed of closely packed cells When these cells are densely packed the structure may resemble sarcoma The embryonal character of the cells is noticeable hence the name fetal adenoma Fetal adenoma is usually a benign lesion but it may give rise to adeno carcinoma carcinoma and possibly sarcoma (From Pfizer *Spectrum* appearing in the J A M A)

In 1934 Hellwig in the *Journal of Endocrinology* demonstrated that calcium chloride administered orally produced hyperplasia and thyroid enlargement in rats He later demonstrated that thyroid adenomata were observed in white rats fed on a calcium rich goitrogenic diet The nodules originate not from fetal rests but from differentiated thyroid epithelium He believed they were due to the same stimulus which causes diffuse hyperplasia and represent an intermediate stage between hyper

Aureomycin and the Thyroid Gland

In the October 29 1954 issue of Science a report was published suggesting that there was a growth stimulating property of the antibiotics which was attributable to the antithyroid effect This study failed to confirm any antithyroid effect of the antibiotic aureomycin This study by Wilson C Grant demonstrated that in no case did aureomycin produce significant change in the weight of the thyroid gland after forty days of feeding it to experimental animal [33] His results differed from those of other (B Calc mick W D Harri and R S Jones *Science* 119 128 1954) not only in degree but in direction Grant concluded that aureomycin failed to produce a significant change in the thyroid gland as to size and actually caused a small but definite increase in the uptake of radioactive iodine [34] The effect of antibiotics on the thyroid gland is being studied further

Case Report HYPERTHYROIDISM IN AN AMERICAN INDIAN
(AN ANTHROPOLOGICAL NOTE)

Interest in thyroid disease never wane The clinical and pathological aspects of hyperthyroidism are enthusiastically studied by the surgeon and internist with equal satisfaction Several years ago a hyperthyroid patient was treated without any apparent difference between him and many others seen previously However during his postoperative stay in the hospital conversation with his immediate family brought to light that he was a full blooded American Indian Never having encountered hyperthyroidism in an American Indian and not having read of a similar case in the current literature it was thought that this case presentation would interest students of thyroid disease This clinical entity is infrequently seen in American Indians For this reason the case is worthy of recording

The degree of the Indian integration into our civilization affects the incidence of such ailments as hyperthyroidism and tuberculosis in this segment of our population the ailments becoming a rough measure of the integration and a matter of anthropological interest

The patient M.S a 55 year-old ironworker was seen for the first time in November 1947 At that time he was under treatment by his family physician for hyperthyroidism He had the classical symptoms nervousness weight loss palpitation tremor exophthalmos and signs of cardiac insufficiency He was classified as a thyrocardiac A B M R taken was +35 He had never been ill until the onset of this illness which according to his history was of two months duration

After an adequate preoperative regimen he was subjected to subtotal thyroidectomy His postoperative course was uneventful and he was discharged from the hospital

During the patient s postoperative period his immediate family was seen for the first time Their general external appearance was similar to that of any other patient However close observation revealed characteristics of the red race This led to questioning and a subsequent lesson on American Indian

The patient informed me that he was a full blooded American Indian of the Mohawk tribe The Mohawks were members of the Iroquois League The strongest

plasia and malignant tumor He later demonstrated that the blood calcium in animals with parenchymatous goiters is double that of those with colloid goiters

There is no doubt that there is an intimate relationship between the parathyroid gland and the metabolism of calcium However, it is not common knowledge that the literature presents evidence to the effect that there is an intimate relationship between thyroid function and calcium metabolism This can be demonstrated when one evaluates the marked



FIG 17 Photomicrograph of a thyroid adenoma demonstrating the separation of the acini by an increase in the supporting matrix due to gelatinous degeneration This increase in supporting matrix and separation compression of the acini identify this lesion as a parenchymatous type of adenoma (Price L W Histology of the Thyroid Gland Medicine Illustrated Feb 1949)

changes which take place in the calcium balance of patients with thyroid disease When thyroid activity is excessive as in thyrotoxicosis, calcium excretion is abnormally high In patients having myxedema the opposite is true, namely that calcium is retained As a general statement, the metabolism of phosphorus parallels that of the calcium In 1942 J D Robertson suggested that thyroxine affected the renal threshold for calcium The excessive secretion of thyroxine in thyrotoxicosis lowers the threshold whereas the deficient secretion in myxedema raises it The corresponding elevated excretion of phosphorus in thyrotoxicosis and its lowered excretion in myxedema are secondary to the changes in calcium excretion The proper administration of iodine in such patients reduces the high calcium output almost to normal and that of phosphorus to normal

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Hemorrhage and Pain in the Thyroid Gland

Thyroid Enlargement Due to Hemorrhage

MANY UNUSUAL occurrences are noted in the thyroid gland. Two of these are sudden thyroid enlargement and the presence of pain in the gland. An unusual cause for a sudden rapid enlargement of the thyroid gland is acute hemorrhage. This type of thyroid enlargement usually is confined to the older patient but may occur in any age group. Of the patients observed by the author five were over sixty years of age and three were in their twenties. All were women. In all but one of these patients a pre-existing enlargement of the thyroid gland was present without toxic symptoms. However, a sudden massive enlargement of the gland prompted medical attention. The reason for the anxiety was difficulty in breathing and wheezing respirations. A detailed report of an unusual case is presented.

Case Report of sudden hemorrhage in a geriatric patient

A seventy three year old housewife was interviewed for the first time in January 1950. At that time she presented the history of an enlargement of the thyroid gland to massive size over a period of four months. She had a small mass in her neck for twenty five years. The sudden growth of the mass in the neck was associated with respiratory distress and wheezing noises with expiration and inspiration. Respiratory relief was obtained when the patient sat up in bed which caused the mass to come forward and cease to compress the trachea.

In April 1950 a total thyroidectomy was performed. Massive cystic adenomata were removed. Within the adenomata were found yellow serous fluid and old blood clot. An elective tracheotomy was performed at the time of operation. The postoperative course was uneventful and the patient was discharged with complete freedom from her respiratory distress.

The operative specimen was carefully studied. The large areas of thyroid tissue were well circumscribed chronic adenomata with cystic degeneration. Yellow serous fluid and old blood clots were contained within the cysts. Arterioles were found showing marked arteriosclerosis as was also evident

of all the Indian groups living east of the Mississippi River were the five tribes composing the Iroquoian League or Five Nations. These tribes, the Mohawk, Oneida, Onondagas, Cayugas and Seneca, held the land from Lake Huron to the Atlantic Coast and south through New York and Pennsylvania. Today the Iroquois live on reservations in New York State and Ontario. Their population is about 1, 000.

The father of the patient under discussion lived on a New York reservation. The son left the reservation as a child and lived in the city. He settled in Brooklyn where there is a small colony of Indians. This colony is located in the less desirable part of Brooklyn. Most of the men in this colony earn their living as ironworkers.

Many of these Indians or their fathers before them adopted names of flower plants or trees. Others are called after parts of a tree as Branch, Leaf, etc. Our patient was named after a part of a plant.

Recently, according to a follow up letter, it has been learned that this patient has developed pleural effusion (1954). The etiology probably is tuberculosis, which disease results in an extremely high mortality in the red race.

Addenda

In the management of hyperthyroidism the Italian school of therapy has utilized reserpine and analogous drugs. They have found that reserpine decreased the patient's anxiety, nervousness and insomnia. The drug was used in conjunction with any other medication prescribed in the treatment of the disease. They found no ill effects when reserpine was given in conjunction with the thiourea compounds.[64]

A recent survey in Tasmania has revealed a thyroid blocking agent as a cause of endemic goiter. It has been found that cows who have been fed one of the Brassicae (chou mollier, thousand headed kale) produce a milk containing an antithyroid substance, namely, 1 5 vinyl 2 thiooxazolidone. This is an interesting revelation since endemic goiter was found in children and as we all know milk is an essential part of every child's diet.[634]

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Fig 18 Thyroid enlargement due to hemorrhage (lateral view)



Fig 18a Anterior view of the same patient as in *figure 18*

clinically by palpation of some of the major blood vessels. The entire pathologic picture was consistent with a rupture of an arteriosclerotic blood vessel with hemorrhage into previous adenomata. The hemorrhage increased the size of the gland until the pressure within the gland equalized or became greater than the systolic blood pressure. When this stage was reached bleeding ceased. The result however was a massive enlargement of the thyroid gland with compression of adjacent structures.

Pain as a Symptom in Thyroid Disease

The presence of pain in thyroid disease is not mentioned frequently among its symptoms. When pain does occur in the gland, it indicates one of two pathologic processes. The first is acute or subacute thyroiditis (strumitis or inflammatory goiter). The second is hemorrhage in the thyroid gland or in an adenoma.

Typical inflammatory processes in the thyroid gland are not as common as other thyroid diseases. For the purpose of this discussion our interest is focused on acute thyroiditis since it is this entity in which sudden pain occurs. Acute thyroiditis usually occurs as a complication of another infection. Pre-existing infections such as rheumatic fever, typhoid fever, measles, acute infections in the teeth, throat, upper respiratory tract or any generalized infection resulting in septicemia may antedate the onset of acute thyroiditis. When acute thyroiditis occurs, pain is a pronounced symptom and tenderness is elicited upon palpation of the gland.[108] (Other instances of thyroid pain will be discussed later.)

The occurrence of hemorrhage in thyroid disease usually occurs in an adenoma. Sudden rapid enlargement of an adenomatous goiter may indicate a rather large hemorrhage. This may occur in an elderly patient with arteriosclerosis. The etiologic basis for this hemorrhage is rupture of an arteriosclerotic vessel. This results in a cystic adenoma filled with blood. Pain occurs with the onset of the hemorrhage. Palpation of the gland elicits a painful response on the part of the patient.

Hemorrhage of small degree may occur in solid adenomata of the thyroid. The hemorrhage results from capillary bleeding and stains the thyroid tissue a deep red or brown depending upon the duration of the hemorrhage. When an adenoma of this type is removed at operation and an immediate cross section view taken, the hemorrhage can be seen upon gross examination. In these patients the occurrence of pain is a prominent feature of the symptom complex. The pain continues even after the acute bleeding has ceased.

Toxic Adenoma (Plummer's Disease)

In toxic adenoma hemorrhage is less frequently seen than in non toxic adenoma In toxic adenoma the tumor alone oversecretes and is therefore



Fig 19 Roentgenogram showing a calcified adenoma of the thyroid removed from a 53 year old housewife with adenomatous goiter

hyperactive The remainder of the thyroid tissue functions normally In primary hyperthyroidism (Graves disease) the entire gland function excessively This fact has been studied and proven by giving patient tracer doses of radioactive iodine *It has been well established by animal* experimentation that the uptake of labeled iodine by the thyroid gland i

a dependable index of the rate of secretory activity of the thyroid cell. Perhaps the fact that in non-toxic adenoma there is a freedom from excessive hyperactivity predisposes the non-toxic adenoma to hemorrhage. This may be based upon the fact that a toxic adenoma utilizes all available



Fig. 20. A 58 year old housewife with typical features of apathetic hyperthyroidism. Note the wrinkled skin, weight loss and the expression of apathy. Arrows point to thyroid enlargement. Note vein displacement to the left side. Basal metabolic rate was +100, pulse 160. Auricular fibrillation was present. Following thyroidectomy the patient had an uneventful recovery. The term "masked" hyperthyroidism has been used as a synonym for apathetic hyperthyroidism.

arterial blood to the area and hence there is no increment of blood available to result in a hemorrhage. Whatever the explanation may be, a serial study of many toxic and non-toxic adenomata discloses that hemorrhage in a solitary toxic adenoma is much less frequently seen than in non-toxic adenoma.

Chronic hemorrhage in the thyroid gland may be identified long after the hemorrhage has ceased. When an adenoma is sectioned and calcium

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Mental Symptoms in Hyperthyroidism

Psychosomatic Symptoms and Borderline Hyperthyroidism

THE SURGEON of yesteryear little realized that posterity would demand a psychiatric knowledge in modern surgery. In the diagnosis and care of hyperthyroid patients the surgeon treads on the confines of the psychiatrist. Although he does not enter this domain, it cannot be denied that in the care of the borderline hyperthyroid patient the surgeon pierces the outskirts of this realm.

Psychosomatic medicine concerns itself with those patients who are neither physically ill nor have an organic mental derangement. These patients are categorized as having "functional illnesses." Most of these individuals have a nervous disposition. A tremor may be present with palpitation occasionally noted. This triad of symptoms labels the patient a hyperthyroid. A basal metabolic rate is taken on the nervous patient. It is usually elevated. Failure to repeat this study does not reveal the error. The diagnosis is apparently correct and the patient is sent to the surgeon for thyroid surgery.

The surgeon now assumes the responsibility. Unless he is alert he will perform a thyroidectomy on a patient whose symptoms will persist or become more marked following surgical intervention.

Neurocirculatory asthenia is the most common disorder confused with hyperthyroidism. These individuals have palpitation, tachycardia, tremor, weight loss and a slightly elevated basal metabolism. Such patients, however, have no eye signs, no increase in pulse pressure or pulse rate. They do have a poor appetite, cold extremities and they demonstrate other manifestations of chronic anxiety.

Psychoneurotic states produced by psychic trauma simulate hyperthyroidism. A patient may have witnessed or been a party to a frightening experience. This factor may precipitate symptoms closely paralleling toxic goiter. This class of patient may have a pre-existing hyperadrenalism. The physical examination of such a person may not confirm the history

is found, it may be postulated that a hemorrhage occurred months prior to the surgical identification of the calcified adenoma Cystic degeneration in a diffuse adenomatous goiter may al o contain calcium often in the shape form and consistency of an eggshell This finding indicates old hemorrhage in a cystic wall or in an adenoma which has undergone cystic degeneration

Apathetic Hyperthyroidism

When a disease is not detected it cannot be treated Apathetic hyper thyroidism is a type of hyperthyroidism which masquerades as heart disease This term is used in contradistinction to the active hyperthyroid patient seen in adult life The apathetic type of individual usually a female appears older than her years The skin is wrinkled and evidence of weight loss is a prominent feature There is no exophthalmos and no visible signs of excessive thyroid activity The striking feature of this type of patient is the apathy revealed in the facial expression Beneath this placid exterior, however the heart rate is rapid and often irregular The B M R is often very high As to the gland itself, it may or may not be enlarged In those patients without thyroid enlargement an exact diag nosis may not be easy Often these types of thyroid patients are not recog nized as such They are treated as cardiacs because of persistent tachy cardia arrhythmias or evidence of decompensation

Although it is true that apathetic hyperthyroidism is not frequently seen nevertheless one should be aware of its existence This type of patient re ponds well to proper thyroid surgery Elimination of the cardiac com plaints in the absence of decompensation almost always occurs For this reason such patients as the e should be properly identified and treated

There are many other aspects of the thyroid symptom complex which will camouflage the underlying hyperthyroidism The unusual feature of this fascinating disease will be discus ed individually in succeeding chap ters

others In such instances it is difficult to sift the mental class of symptoms from the hyperthyroid group This type of patient however presents many signs of hyperthyroidism which categorize the disease Thus even if the mental complaints are attributed to hyperthyroidism at least the major underlying pathological condition has been identified

Upon the thyroid surgeon rests the burden of separating borderline hyperthyroidism from functional disorders His perspicuity and decision will save the neurotic from a needless thyroidectomy even as he can eradicate the stamp of hypochondriasis from a patient with mild hyperthyroidism

In a study of patients with hyperthyroidism attention was called to the close association between psychosomatic symptoms and borderline hyperthyroidism The fine differentiation between true hyperthyroidism and chronic fatigue or neurocirculatory asthenia has been stressed Additional observation of thyroid patients brought to light the frequency of mental symptoms in hyperthyroidism The experience stimulated an interest in the unusual complaints manifested by patients with severe hyperthyroidism

Phobia as a Symptom in Hyperthyroidism

During the past ten years (1947–1957) 356 primary hyperthyroid patients were carefully questioned as to the presence or absence of phobias[93] No leading questions were asked the only suggestive questioning was "Are you very nervous?" By careful interrogation the presence of a phobia was elicited without difficulty These phobias were accordingly grouped as follows

Type of Phobia	No. of Cases	Sex M	Sex F
Claustrophobia (fear of confined places)	135	6	129
Monophobia (fear of being alone)	66	—	66
Ochlophobia (fear of crowds)	45	3	42
Acrophobia (fear of high places)	42	—	42
Anthrophobia (fear of men)	15	—	15
Gynophobia (fear of women)	22	22	—
Hematophobia (fear of blood)	6	—	6
Nyctophobia (fear of the dark)	6	—	6
Zoophobia (fear of animals)	12	—	12
Taphephobia (fear of being buried alive)	4	4	—
Astraphobia (fear of thunder)	3	—	3

From this survey it can be appreciated that phobia in excessive thyroid metabolism is not rare It may easily be overlooked if the physician fails to recall that mental symptoms are often present in patients with hyperthyroidism

of tremor sweating and tachycardia The gland may be normal to inspection and palpation without any audible bruit The value of the pulse rate which is increased in hyperthyroidism is noteworthy Psychic factors may cause a temporary elevation whereas hyperthyroidism maintains a constant elevation of the pulse rate A fact to remember is that the toxic goiter patient is usually older than the neurotic individual It has been observed that patients with true hyperthyroidism often have a tendency to cry spontaneously without apparent cause

When the basal metabolism has been elevated on the initial reading technical inaccuracies may be the cause The nervous individual should be informed of the procedure and his cooperation obtained As a generality it may be stated that cooperation and relaxation are less frequently obtained with psychoneurotic patients than with hyperthyroid individuals Repetition of the test each morning until a satisfactory technical reading is obtained may reward the observer with a normal basal metabolic recording Radioactive iodine uptake is a very valuable diagnostic procedure in determining the presence of true hyperthyroidism [90, 93] (See other diagnostic aids)

Another important differentiating observation is the apparent improvement when these functionally disturbed patients are hospitalized When these persons are liberated from familial entanglements relief occurs within a few days Freedom from noxious mental stimuli eradicates the tachycardia and nervous symptoms

When persons with mental unrest have been convinced of the functional nature of their complaints and are assisted by competent helpful psychiatric suggestions improvement is noted With the aid of a psychiatrist the so called hyperthyroid patient undergoes a complete metamorphosis All patients suspected of mild hyperthyroidism do not fall into the category stressed even as the diagnosis between a functional disorder and borderline hyperthyroidism is not as facile as outlined above Each individual is a singular problem There is no one diagnostic pattern applicable to all patients

Caution is advised against the other extreme of failing to recognize a true borderline hyperthyroid patient To brand such a patient a hypochondriac a malingerer or a neurotic may produce deleterious results It must also be realized that hyperthyroidism is a manifestation of a constitutional disease and as such may produce unusual psychic reactions Although no characteristic psychic reaction is indigenous of hyperthyroidism many of these patients have acute delirium Some patients with long standing hyperthyroidism may manifest toxic exhaustion psychosis and others a manic depressive reaction

True mental disease may occur in the hyperthyroid individual as in

she commenced to dislike herself because she menstruated. Over a period of months she developed a hatred of menstruation as a womanly trait. Finally a homosexual temperament and characteristics became manifest. Another female patient feared the sight of blood to an unprecedented degree. She refused to eat red meat because of the blood. Fainting at the sight of someone bleeding was a common experience with her. In spite of this she adapted herself well to her menstrual cycle. Following thyroidectomy and prolonged psychological therapy her hemophobia disappeared.

Hyperthyroidism and Neurosis

A purposeful study of the mental attitude of the hyperthyroid patient has revealed an interesting psychic component in these individuals. Two results of this study were previously discussed. One of these distinguished psychosomatic symptoms from borderline hyperthyroidism. The other unfolded major phobias in patients with primary hyperthyroidism.[90-93] A continuation of this study concerned the presence of neurotic symptoms in hyperthyroid patients, the existence of hyperthyroidism in neurotic individuals, and the relationship between this mental state and organic thyroid disease. Prior to discussing these three categories of patients thought must be given to the present concept of neuroses and the abnormal influence of hyperthyroidism on somatic physiology.

A neurosis must be considered as a definite mental illness frequently encountered in modern medicine. Mental illnesses in general must be interpreted as the inability of the individual to mold himself into the environmental pattern. Some serious mental ailments have been labelled as psychoses, milder illnesses with a mental component have been called neuroses or psychoneuroses. In most cases of neurosis the person is made sensitive to or has been conditioned by inhibited childhood experiences. The disease becomes manifested by an acute emotional crisis. Anxiety is the root of psychoneurotic reactions. The patient is conscious of his anxiety state and is confronted by it with a demand for solution. He then attempts to follow some method leading to the solution of his problem. Inadequate handling of the situation results in conversion reaction or conversion hysteria. This conversion of anxiety into disordered functions of the organs or parts of the body is reflected in a train of symptoms which labels the patient a neurotic.

The neurotic symptomatology is limitless. Symptoms are fundamentally characterized by intellectual and emotional reflections usually given the general label of nervousness. Complaints are identified by the title of nervous stomach, irritable heart, irritable colon, etc. Other symptoms reflect emotionalism in the guise of fears, doubts, anxieties, compulsions

The above study indicates that the most frequently encountered fear is claustrophobia The author remembered quite vividly a 26 year old white female with severe hyperthyroidism She developed a Bell s palsy for which diathermy was advised It was impossible to treat her because she could not tolerate the diathermy pads on her face The pads gave her a sense of crowding and fear similar to being in a closed room She was quite intelligent a college graduate and volunteered the information that she had claustrophobia

The second most common phobia in this series was the fear of being alone Sixty six of the patients studied offered this complaint One middle aged lady could not remain in her own home alone When forced to do so she would telephone her friends and talk for hours in trivial conversation Following thyroidectomy she became a taciturn matron

The opposite situation was observed in 45 people These individuals feared crowds and preferred to remain at home This phobia often resulted in a pallid complexion because of the lack of sunshine Most of these people would venture out of the house only in the darkness of evening

Forty two patients had acrophobia One patient a 38 year old housewife, lived in an elegant 5 room sixth floor apartment overlooking the river Her fear of high places was so severe that she would not look out the window although the view was most beautiful She constantly quarrelled with her husband since she wanted to move out of the apartment The scarcity of living accommodations was the source of the familial discord

A fearful dislike of the opposite sex was unfolded in 37 cases Fifteen women and twenty two men were so afflicted A patient, recently seen in consultation with an internist, could not eat in the presence of a woman He could not give the reason for his behavior but it was a constant experience One day his buddy invited him to his home for dinner He was assured that no women would be present During the course of the dinner the friend s young married sister arrived unexpectedly his appetite left him immediately He could not take another mouthful of food Following adequate thyroid surgery and psychiatric therapy, he married eventually becoming a proud father

Other types of phobias in these patients were fear of blood fear of the dark thunder and fear of animals A most interesting hyperthyroid person was a middle aged man who had taphephobia His fear of being buried alive was so fixed in his mind that he left instructions in his will for an autopsy on his body Another patient had violent fear of thunder During a rain storm she would hide under her bed or run down the cellar to hide until the storm subsided

Six patients exhibited intense fear of blood All were young women, one of whom became frightened at her own menstrual flow As time went on

inaccuracies are frequent. For this reason radioactive iodine uptake is a more valuable asset in diagnosis than the basal metabolic rate.

The patient with true hyperthyroidism may be often overlooked because of the bizarre symptoms occasionally encountered. In the classical hyperthyroid case no difficulty arises in making the diagnosis. It is the borderline patient who presents the difficulty and is often mishandled.

Case 1. An illustration of this type of patient concerns a 52 year old widow who had a thyroidectomy 5 years before her present complaint. The present illness of 6 months duration consisted of occasional trembling of arms and legs, intolerance to heat, frequent perspiration and emotional instability characterized by crying without apparent cause. She was sent to a psychiatrist who decided she was not neurotic as previously labelled by several physicians. At the time of her examination the significant findings were a rapid pulse of 120, B.M.R. +41, blood pressure 130/70. The left lobe of the thyroid was enlarged to 4 to 5 times. It could readily be seen and when called to the attention of the patient she acknowledged seeing its existence shortly after her previous thyroidectomy. Her complaints were attributed to a psychoneurosis and she went from doctor to doctor until finally she was referred to a psychiatrist who believed she had organic disease. The diagnosis of hyperthyroidism was made and the patient was prepared for operation. At operation the left lobe of the thyroid was removed. Following surgery her condition markedly improved. She was free from her previous complaint and has now returned to the normal duties of a housewife.

Case 2. A 19 year old unmarried woman was treated for 6 years because of gastrointestinal symptoms characterized by nausea, sense of fullness and occasional diarrhea. In addition to this she was extremely nervous, very irritable and complained of cardiac palpitation. At the time of examination many of the above symptoms were confirmed, also the fact that she had a phobia which was reflected in the fear of crowds (ochlophobia). Her B.M.R. at this time was +25, pulse 100 and blood pressure 140/70. This patient was labeled a neurotic and was sent to a psychiatrist by an internist. It was only after the psychiatrist had adequately studied the individual that the diagnosis of hyperthyroidism was made. She was subsequently operated upon and at the time of this writing which is 5 years following operation she is a changed person without any of the previously mentioned complaints.

Men of medicine and surgery who are conscious of the existence of thyroid disease often become overzealous in their diagnosis. The presence of nervousness, irritability and palpitation indicts the patient as having hyperthyroidism. This triad of symptoms may result in a thyroidectomy if the surgeon is not alert. Undoubtedly it has been the sad experience of many surgeons to have operated upon patients with true neurosis.

Case 3. A 25 year old woman employed by a telephone company was seen in consultation because of supposed hyperthyroidism. The patient was very nervous and irritable, had palpitation of the heart and a marked tremor. Her B.M.R. was +30. However, after a series of readings it was found to be +5. Her pulse was normal, the blood pressure was normal. Thyroid was normal to palpation except for the isthmus which was slightly larger than normal. The clinical picture was not true hyperthyroidism. Finally consultation with a psychiatrist elicited the diagnosis of

and obsessions. An adequate history brings to light many hidden symptoms which formerly were simply called nervousness.

Nervousness is a cardinal symptom in patients with toxic hyperthyroidism. Excessive thyroid activity affects every organ of the body. Hence tachycardia and gastrointestinal complaints are similar to those symptoms manifested by the neurotic individual. To this symptomatology add phobia which has been considered as a new symptom in hyperthyroidism. Fear being a common attribute of the neurotic patient, the overlapping of symptomatology reflects the contiguous confusion in differentiating neurosis from hyperthyroidism.



FIG 21 Normal thyroid showing microscopic view of follicles filled with colloid (Courtesy of Romaine Pierson Publishers, Manhasset, N. Y.)

Very often the surgeon must assume the responsibility of differentiating the true hyperthyroid patient from the neurotic one. The psychoneurotic person may have witnessed or been a party to a frightening experience. This factor may bring forward symptoms closely paralleling toxic goiter according to the mechanism previously mentioned. The physical examination of such a person may not confirm the history of tremor, sweating and tachycardia. The gland may be normal to inspection and palpation without any audible bruit. As mentioned previously the value of the pulse rate and pulse pressure is noteworthy. Psychic factors cause a temporary elevation whereas hyperthyroidism maintains a constantly elevated pulse rate. Emotionalism manifested by spontaneous tears without apparent cause is frequently elicited in true hyperthyroidism. Elevated basal metabolic rate in neurotic patients may occur for several reasons since technical

onstrates the presence of both neurosis and hyperthyroidism in the same patient. These cases argue for perspicuity and care in diagnosing hyperthyroidism. They call to mind the pitfalls in labeling a person a neurotic without adequate study.

Modern surgery and psychiatry have become necessary supplements to the advancing knowledge of disease. In many cases the combination of thyroidectomy and intensive psychotherapy results in a disappearance of thyroid complaints and neurotic manifestation. The above case histories emphasize the need for an adequate case history, physical examination and laboratory studies in both neurotic and hyperthyroid patients. The dual cooperation between the surgeon and psychiatrist may save a neurotic patient from a needless thyroidectomy, even as the surgeon's scalpel has eliminated prolonged psychological treatment of patients with hyperthyroidism.

Addenda

In recent months we have had available certain "anti neurotic" drugs such as frenquel (azacyclonol hydrochloride) which have been used as therapeutic tests and as an aid in differentiating the neurotic from the hyperthyroid patient. Drugs such as these have had beneficial effects on neurotic patients who become emotionally stable under their influence.

anxiety neurosis Thus it transpired that a patient referred by an internist for a thyroidectomy had in reality a neurosis

It must not be forgotten, however, that true mental disease may occur in the hyperthyroid individual even as it may occur in any other person When this situation exists it is difficult to sift the mental class of symptoms from the hyperthyroid group Where a true mental disease exists in the hyperthyroid patient it is always found that there are many signs of hyperthyroidism which will categorize the disease Thus even if the mental complaints are attributed to hyperthyroidism, the major underlying pathology will reveal itself by careful study



FIG 22 Primary hyperthyroidism (exophthalmic goiter) showing microscopic view of diffuse hyperplasia and papillary projections into acini indicative of accelerated glandular activity (Courtesy of Romaine Pierson Publishers Manhasset N Y)

Case 4 A 25 year old unmarried woman presented the complaints of nervousness *palpitation and fear of crowds This was of 6 months duration* Her pulse was 110 blood pressure was 145/70 B M R was +28 Examination of the thyroid revealed an enlarged right lobe and a slightly enlarged left lobe The diagnosis was adenomatous goiter with secondary hyperthyroidism In addition to this complaint the patient had typical symptoms of anxiety neurosis She was seen in consultation with a psychiatrist who treated her for neurosis Both the internist and the psychiatrist prepared her for operation

When she had been successfully prepared thyroidectomy was performed followed by *an eradication of thyroid symptoms The psychiatrist then* continued to treat her for neurosis The thyroid symptoms disappeared soon after the operation but the neurotic symptoms manifested themselves as late as 4 months following surgery

These cases illustrate several instances of problems in the differential diagnosis between neurosis and hyperthyroidism The last example dem

potassium thiocyanate in the treatment of arterial hypertension There are many contraindications to and side effects of thiocyanate therapy If the patient is not under constant observation the drug should not be administered Specifically blood thiocyanate determination is the only safe measure against serious toxic manifestations

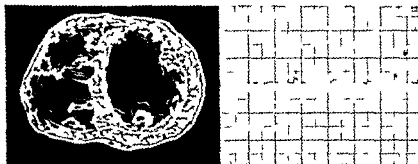


FIG 77 Diagrammatic representation of a myxedema heart in cross section and the concomitant electrocardiograph finding The anatomic section demonstrates general cardiac dilatation and enlargement of all the chambers of the heart The inner white line represents the normal size of the heart The electrocardiograph reveals flattened T waves Cardiac impairment is the most frequent and prominent feature of myxedema (called myxedema heart by Zondek) A myxedema heart is characterized by generalized enlargement and dilatation of all four chambers The muscular tonus of the heart is decreased the pulse weakens and the circulation becomes slow The blood pressure is not always low but may be maintained The T waves in the electrocardiogram show changes which may be flattening or even inversion Blood studies unfold a secondary anemia high cholesterol and low levels of protein-bound iodine (Courtesy of Warner-Chilcott Laboratories)

Case report The literature contains a report of acute goiter during thiocyanate therapy for hypertension [14] In this case the large gland regressed and the associated hypothyroid phenomenon subsided under treatment with thyroid extract and iodides

The patient reported here had a previous hemithyroidectomy performed for an adenoma in 1917 Exploration of the opposite lobe at the time of operation confirmed the absence of any left-sided adenoma It is acknowledged that a *microscopic* adenoma may have been unidentified at operation Subsequent to her thyroidectomy the patient was given potassium thiocyanate and continued to take it without proper supervision She developed a sensitivity to the drug which was controlled by an antihistamine preparation

In November 19.3 she manifested clinical symptoms of myxedema and a nontoxic adenoma was found on the side opposite to her previous hemithyroidectomy It is believed that all of these manifestations *including* the thyroid enlargement are the results of the improper use of potassium thiocyanate



Fig 25 Patient with myxedema (left) and the same patient after the administration of proloid for several weeks The thyroid gland controls the body so effectively that its failure to function affects the entire organism even in an adult In myxedema there is a generalized diminution in human function so that with severe myxedema the body is practically in a state of hibernation The metabolic rate may fall to below 35 oxidation decreases and the metabolism of protein minerals carbohydrates and fats falls rapidly Myxedema ascites may result with an associated retention of water salt and protein in the intracellular fluids (Courtesy of Warner Chilcott Laboratories)



Fig 26 Hands of a female patient showing the changes resulting from myxedema The skin is coarse scale like and thickened in appearance The fingernails are retroverted (Graham E A Surgical Diagnosis Philadelphia W B Saunders Co 1930)

With the objective in view the following is a general method of administering thyroid extract according to Means

Age	Gr per Day
Up to 4 mo	$\frac{1}{10}$
4 to 8 mo	$\frac{1}{4}$
8 to 12 mo	$\frac{1}{3}$
1 to 2 yr	$\frac{1}{2}$–1
2 to 4 yr	$\frac{1}{2}$–2
4 to 12 yr	1–4

In adult myxedema the underlying foundation of the anatomical and physical structure is not impaired and excellent effects from thyroid substitutive therapy are regularly obtained. Small doses must be employed at first and increased slowly at sufficiently long intervals until the symptoms are brought under control. Thereafter the patient will probably have to continue indefinitely on a maintenance dose of the hormone.

The thyroid requirement is usually found by beginning with doses of ¼ gr per day and after three weeks if no toxic manifestations have occurred doubling it. In this way the maintenance dose is found most often in the range of 1½ to 3 gr daily. Juvenile cases are treated in the same way but their cerebral tolerance to thyroid extract is delicate and the effects of each increment in dosage must be observed carefully.

Means made a statement concerning myxedema (Gull's disease) which is most worthy of repetition.[14] He stated: "If one had been unable to arrive at a positive diagnosis in a myxedema-like picture the presence or absence of characteristic response to thyroid would be of diagnostic significance. If while being treated for definite hypothyroidism with thyroid extract the patient went into Addisonian crisis the diagnosis of hypothyroidism due to primary hypopituitarism would be established."

Ascites in Myxedema

There have been only a few cases of ascites due to myxedema reported in the literature.[310] This complication may be a symptom of myxedema itself just as the periorbital or pretibial edema and pleural and pericardial effusions. It has been postulated that the cause for these changes is an alteration in the body proteins. However it must be remembered that ascites may be an expression of congestive heart failure due to myocardial degeneration secondary to myxedema or of coronary artery disease which has been found to be a frequent concomitant to myxedema. Differential

Mental Symptoms in Myxedema

In the neglected cases of myxedema (Gull's disease) a high incidence of psychosis is often manifested As early as 1883, it was recognized that these mental symptoms were a definite clinical entity and contemporary psychiatrists would label this clinical picture as "myxedema madness" Some of these patients present a symptomatology of schizophrenia[3] These unfortunate individuals may suffer from delusions, hallucinations, and mental deterioration Even in these modern times it is not rare to encounter patients with a psychosis secondary to myxedema Paranoid features are often manifested by many patients with advanced myxedema Prior to the knowledge of the hormonal nature of their disturbances many of these patients were considered to be clinical examples of primary mental disease

The increasing knowledge of the relationship between thyroid function and the brain is the basis for a new re evaluation of the etiology of certain mental diseases Many current authorities in the field of psychopathology have postulated that many psychoses may find their origin based on a neuroendocrine imbalance Kraepelin in 1917 wrote "cretinism is one of the few forms of insanity in which we can obtain at any rate an approximate idea of the connection between cause and effect[3 3] We have both in cretinism and myxedema examples of the fact that the destruction of a small constituent portion of the body may bring about severe disturbances in its whole economy and more especially may be the cause of insanity Our knowledge of such relationships is of very recent origin It is, therefore, conceivable that similar relations may some day be discovered in other forms of insanity

When hypothyroidism is responsible for cerebral disfunction the administration of thyroid extract in small doses may have a dramatic beneficial effect This is especially noted in the infantile or juvenile patients in whom there is the best chance for recovery under adequate treatment McGavack has stated "Delays in beginning treatment affect the outlook for mental achievement more than the outcome for physical development"[67] The effectiveness of thyroid extract is very well known The only *danger associated with the administration of thyroid extract is the possi*bility of overdosage Means has found that a profound physiologic change can be produced in a patient by the administration of thyroid extract[19] [319] This is especially true in children In cretinism the amount of thyroid extract to be given depends upon the age of the patient As a guide it may be stated that the amount of thyroid extract is such that will give the maximum therapeutic effects without even the slightest toxic manifestation

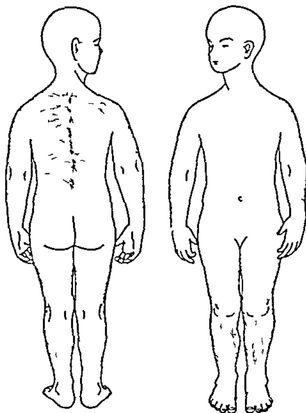


Fig 28 Drawing illustrating the distribution of hair in hypothyroid children This unusual but typical hirsutism involving the back, shoulder, outer aspects of the arms and legs and to a lesser degree the sides of the face may be a manifestation of hypothyroidism in children (Perloff W H Hirsutism J A M A 157 No 8 1955)

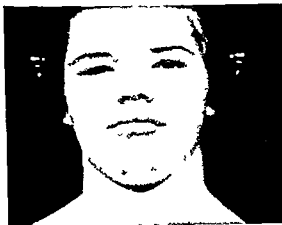


Fig 29 Juvenile myxedema with goiter (Courtesy Warner Chilcott Laboratories)

diagnosis naturally is quite difficult. However, a study of the venous pressure and ascitic fluid high in protein and specific gravity would favor the belief that the ascites was a symptom of myxedema. Contrariwise, an elevated venous pressure and ascites with a low protein and specific gravity (transudate) would lead one to favor the presence of congestive heart failure. In either case the treatment must be outlined with great care. Small doses of thyroid extract are important for the management of primary myxedematous fluid accumulation. On the other hand digitalis, (its purified derivatives) diuretics and salt restriction are indicated in congestive heart failure.

Endemic and Sporadic Cretinism

Several centuries ago Felix Platter (Platerus 1536–1614), who occupied the chair of medicine at the University of Basle, Switzerland, was one of the first men of medicine to give an accurate clinical description of cretinism and to note its relationship to endemic goiter.[30] He stated: "Wherefore the disease is frequent in certain regions; in the beginning they write of it in Egypt and in Valesia Canton Bremis, as indeed I have seen it myself, and in the Carinthia valley called Bintzgerthal many infants are wont to be afflicted, who besides their innate simple mindedness, the head is now and then misformed, the tongue immense and flabby, dumb, a struma often at the throat; they show a deformed appearance, and seated in solemn stateliness, staring, and a stick resting between their hands, their bodies twisted variously, their eyes wide apart, they show immoderate laughter and wonder at unknown things."[30]

In certain areas of the world where simple goiter has been severely and continuously endemic over many generations the children of goiter bearing parents may be born with an almost complete lack of thyroid secretion. When this sad situation occurs in a child he is a goitrous degenerate and exhibits some of the typical physical and mental symptoms of hypothyroidism. *This condition is known as endemic cretinism (in Europe referred to as cretinic degeneration).* It is most important to distinguish this from childhood myxedema (sporadic cretinism) with which it is often confused, especially in infancy.

Endemic cretinism and sporadic cretinism (infantile or childhood myxedema) are two separate and distinct thyroid diseases unrelated except for the fact that they both involve hypothyroidism. They differ markedly in their etiology, pathology, symptomatology, and in their response to proper treatment. Under the term endemic cretinism is classified all those cases resulting from over more than one generation of insufficiency of iodine and in whom the thyroid gland is almost always enlarged. These

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Hyperthyroidism, Puberty and the Reproductive Process

Physiological Enlargement of the Thyroid

As an expression of the normal physiological development many young girls show evidence of a slight to moderate soft enlargement of the thyroid gland at or about the age of puberty. This enlargement, which is an expression of normal thyroid activity, is of short duration, transitory in type and almost always leaves no residual thyroid damage. On rare occasions the thyroid enlargement, however, may persist after puberty and may be consistent with normal health and activity. Such enlargement of the thyroid gland are not pathological and cannot accurately be indicted as the precursors of thyroid disease which may occur in later life. An analogous alteration in the size of the thyroid gland is noted due to menstruation and pregnancy. During these physiological endocrine functions (menstrual cycle and pregnancy) an alteration in the size of the thyroid gland must be regarded as a normal accompaniment of sexual and reproductive activity. It is for this reason that the literature often refers to this type of thyroid enlargement as physiological, adolescent, school, or puberty goiter. These alterations in the thyroid gland are so common during puberty that they are rarely noticed and often dismissed without comment in a discussion of thyroid disturbances.[103, 1[illegible]]

The onset of puberty in a girl, like pregnancy and lactation, places an added burden upon the thyroid gland. If during this period a young girl has a deficiency in dietary iodine, the thyroid hormone may become temporarily disturbed due to iodine inadequacy. Thyroid enlargement may be the response to this physiological iodine inadequacy. However, when the limited iodine intake no longer exists and a sufficient amount is available, the thyroid enlargement may subside and the gland will assume its normal size, shape and consistency. On the other hand, if the iodine supply is really sufficient, there is enough available to meet the demands of the body in all phases of its development. Therefore there will be no evidence of this so-called physiological enlargement of the thyroid gland.

Succinctly, therefore, it may be stated that physiological enlargement

patients are always born of goitrous parents. Under the term childhood myxedema (sporadic cretinism) are categorized those patients in which the etiology is the same as in adult myxedema. This type of myxedema is not due to an iodine deficiency but to complete atrophy or congenital absence of the thyroid gland. Sporadic cretins are rarely born of goitrous parents and in view of the atrophy of the thyroid gland this condition must be considered as non goitrous.

Skin Test for Myxedema in Children

In certain problem patients when a diagnosis of myxedema is difficult or borderline, a study of the skin may be revealing.

Biopsy specimens of dermal connective tissue may reveal alterations pathognomonic of hypothyroidism in children. Diagnostic histopathologic changes were observed in 15 of 26 patients with definite hypothyroidism and in 8 of 21 individuals with the suspected disease. No changes were observed in 52 euthyroid children, reported Dr. Henning Andersen and associates of the Dronning Louises Borneho pital and the University Institute of Medical Anatomy, Copenhagen.[5,8] Criteria of positive specimens include increased numbers and granulation of mast cells, edema, altered state of blood vessels and texture of fibrils, and pronounced degrees of metachromasia and keratosis. Failure to observe metachromasia or other tissue changes in all myxedematous patients may be due to effects of previous thyroid therapy or to pituitary insufficiencies.

In some children the first sign of thyroid deficiency may be a hyperkeratosis of the elbows and knees manifested by stubbornly dirty patches for hypothyroidism assumes many forms.

To diagnose the condition correctly and as early as possible, more than the classical tests are often employed. A simple and readily available diagnostic test for borderline hypothyroidism consists of administration of small doses of thyroid over a period of several weeks.



Fig 30 Primary hyperthyroidism before puberty Patient was a 10 year old girl with classic hyperthyroid symptomatology B M R +70 Arrows indicate site of enlarged thyroid gland (Graham E A Surgical Diagnosis Philadelphia W B Saunders 1930)

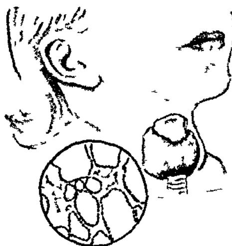


Fig 31 Nontoxic goiter before puberty Insert is artist's drawing of microscopic section showing nontoxic goiter (From Pfizer *Spectrum* appearing in the J A M A)

of the thyroid during puberty is a normal manifestation When this type of physiological enlargement is seen it should not be dismissed as an inevitable accompaniment of puberty but thought must be given to the possibility of a borderline iodine deficiency which can easily be corrected by the administration of iodine orally

It may be the erroneous belief of some that toxic goiter is a disease of adults Although it is true that hyperthyroidism in children is not very common, nevertheless it does occur Usually the initiating factor of hyperthyroidism is contained within the syndrome of primary hyperthyroidism and *is often more acute than that observed in adults* The exact etiology of hyperthyroidism in children like that in adults, is not clearly understood Predisposition may play an important part Superimposed upon this congenital foundation an exciting cause may initiate the disease Among these exciting causes attention is called to psychic trauma over exercise, and focal or general infections The incidence of *hyperthyroidism* in children is usually based upon the number of cases in proportion to the number of adults having the disease in a given series In the literature written on this subject the ratio varies between 1 and 5 per cent [103] Seventy per cent of all cases of hyperthyroidism in children occurs during puberty When a child approaches puberty therefore many symptoms may be erroneously interpreted or discounted as insignificant For this reason a resume of the salient features of hyperthyroidism before puberty is not *unimportant*

Of the classical symptoms of hyperthyroidism the four most frequently seen in children are nervousness tachycardia exophthalmos and enlarged thyroid

In considering nervousness a child may be observed to be restless in bed This type of restlessness may or may not be associated with enuresis Hyperactivity, restlessness and emotional instability are equivalent to nervousness Falling out of bed sighing and crying during sleep are other expressions of nervousness These above mentioned nervous equivalents with or without nervousness and irritability may be the expression of an initiating phase of hyperthyroidism in children

Tachycardia is a constant finding in hyperthyroid children It is rarely *a subjective symptom The heart rate varies between 90 and 180 beats* per minute There is a constantly elevated pulse pressure Exophthalmos is not a common sign When it is present it is of slight to moderate degree It is rarely as severe as that seen in adults with severe hyperthyroidism

In almost all hyperthyroid children the thyroid gland although not *greatly* enlarged is visibly or palpably larger than normal When an adenomatous goiter with secondary hyperthyroidism is the basic pathology, then the gland is readily palpable and visibly enlarged

a complete study as to the possibility of hyperthyroidism Overactivity constant tachycardia with a loss of or a failure to gain weight are symptoms demanding investigation of hyperthyroid function

The differential diagnosis between mild rheumatic fever mild chorea and mild hyperthyroidism in children is most difficult Laboratory studies are an aid but do not enable an exact diagnosis to be reached with ease



Fig 32 Cystic hygroma of the neck (congenital cystic lymphangioma) to be differentiated from congenital goiter Hygroma develops soon after birth and becomes quite large It arises from dilated lymph vessels rarely causes symptoms of tracheal compression but is easily inflamed producing redness of the overlying skin This cyst usually contains clear serous fluid Branchial cysts contain crumbs or sebaceous material

A most reliable diagnostic test is the beneficial response to iodine therapy (see previous discussion on Physiological Enlargement of The Thyroid) In order to arrive at a diagnosis of hyperthyroidism one must eliminate paroxysmal tachycardia anemia anxiety neurosis malnutrition and intestinal parasites Other conditions may simulate an enlargement of the thyroid gland e g a cervical fat pad may give the false impression of thyroid enlargement In thin children the normal thyroid because of deficiency of adipose tissue may become prominent and be mistaken for an enlarged thyroid gland A congenital thyroglossal cyst may be misconstrued as an enlarged thyroid lobe A cyst is usually smaller than the

There are certain symptoms found in hyperthyroid children which are found in adults They however are somewhat altered in the younger group *For example tremor when present closely resembles the purposeless movements of chorea* Gastrointestinal symptoms, as nausea, vomiting, diarrhea and abdominal pain occur in about 20 per cent of children with hyperthyroidism On occasion a child may be suspected of having an acute surgical condition within the abdomen when in reality the underlying pathology is hyperthyroidism

Muscular weakness may occur as an initial hyperthyroid complaint This is similar to that seen in adults with hyperthyroidism but to a lesser degree Quadriceps femoris muscular weakness can be demonstrated by asking the child to step up on a chair or by keeping his leg extended while sitting in a chair

Other symptoms seen in adults are absent in children The most important of these symptoms hyperhidrosis is not prominent in childhood hyperthyroidism Another group of symptoms are found only in children For example growth disturbances may occur Skeletal growth is more rapid than average in hyperthyroid children Epiphyseal ages are accelerated teeth develop prematurely and a demineralization of the body skeleton may be noted In toxic female children ovarian function is suppressed and secondary sexual characteristics develop slowly Menstruation is inhibited and often absent In boys there is a retardation of sexual maturity

An additional feature of hyperthyroidism before puberty is that many hyperthyroid children develop their symptoms after an infectious disease The most common infectious diseases are measles and pertussis Another aspect of the clinical picture of hyperthyroidism in children is the possibility of having a patient born a cretin with a goiter and remain a cretin until hyperthyroidism develops Psychiatrists have emphasized the fact that behavior disorders in children may be an expression of disturbed thyroid function The proper evaluation of and a satisfactory differential diagnosis of symptoms are most essential in arriving at the diagnosis of *hyperthyroidism in children*

Diagnosis and Differential Diagnosis[1]

The diagnostic tests for children are essentially the same as those for an adult An exception is that radioactive iodine is rarely given to children *for diagnostic purposes* The B M R however is always looked upon with suspicion and doubt because of inaccuracies both technical and otherwise In typical cases of hyperthyroidism the diagnosis is not difficult It is the early stages of hyperthyroidism that are overlooked Any child with an enlarged thyroid with nervousness or irritability deserves

thyroid gland itself and is located above the thyroid area There is little if any movement of a cyst with deglutition Any movement when present is lateral rather than vertical as is usually seen in the thyroid gland

Congenital pop eyes may erroneously suggest the exophthalmos of hyperthyroidism The congenital deformity usually occurs in myopia in conjunction with a shallow orbit or an increased anteroposterior dimension of the eyeball A consultation with an ophthalmologist is necessary in some cases to eliminate hyperthyroidism

From this diagnostic review it can be appreciated that often it is not easy to arrive at a proper diagnosis of early hyperthyroidism before puberty

Treatment

The introduction of the newer antithyroid drugs has resulted in a change in the management of hyperthyroidism in children Medical management is often attempted prior to more radical therapy In the initial stage of the disease complete physical and mental rest is necessary All stimulants are avoided including nonalcoholic beverages which contain caffeine In addition to these general measures propylthiouracil etc is administered The antithyroid drugs are well tolerated by children The usual precautions similar to the administration of the drug to adults are taken The dose may vary between 100 and 200 mg daily

There is a great tendency to spontaneous remission of hyperthyroid symptoms in children therefore the results of medical treatment should be guarded Other objections to the use of the thiourea drugs are the possible development of leukopenia agranulocytosis and their potential carcinogenic action The hyperplasia they produce in the thyroid gland approaches malignant changes in many patients

The hope that the antithyroid drugs would be a substitute for thyroidectomy has not materialized When surgical treatment is decided upon a preoperative administration of Lugol's solution 10 drops daily with or without the antithyroid drug is given The Lugol's solution is usually given for 3 weeks prior to operation The use of organidin in the same dosage as Lugol's is equally as efficacious

Although thyroidectomy does not correct the primary underlying cause of hyperthyroidism nevertheless it has been the accepted therapy for decades There is disagreement as to the amount of thyroid to be removed in a child as well as to the frequency of persistent hyperthyroidism and myxedema following operation It is believed by many that the same amount of tissue should be removed as in an adult thyroidectomy Recurrence of myxedema is not an uncommon postoperative experience There is no indication that the preservation of more or less of the gland



FIG 33 4 A 2 month old male infant with congenital pop-eyes
B Closer view of infant showing that the proptosis is more marked on the left side
C Lateral view of the same infant with congenital proptosis

for one year prior to delivery Hydramnios developed and the woman went into labor, delivering a girl of 34 weeks gestation weighing 4 lb 1½ oz (1,843 Gm) The baby was born with a diffusely enlarged thyroid that was firm and nodular The thyroid was so large that the head was held in retraction When the infant began to have difficulty in swallowing 2 drops of Lugol s iodine solution were given daily Episodes of cyanosis and difficulty in breathing necessitated frequent suction and oxygen The thyroid enlargement subsided and the head retraction position gradually disappeared with the diminution in the size of the thyroid gland The infant received desiccated thyroid substance 5 days after birth The administration of this extract was stopped when the thyroid enlargement disappeared on the 36th day Several days later a slight exophthalmos appeared A few weeks later, when the baby was treated with sulfadiazine and sulfasuxidine because of diarrhea and cellulitis the thyroid again became diffusely enlarged and severe head retraction recurred When the administration of the sulfonamide preparations was discontinued the head retraction vanished along with the thyroid enlargement

Although most mothers treated with thiouracil give birth to normal infants about 20 to 30 per cent apparently show some effect on the fetal and neonatal human thyroid as a result of this drug Furthermore it has been reported that, in mothers receiving iodine with the antithyroid drugs no abnormalities occurred in the offspring This case report by Perlman negates this observation In fact, goiter is known to occur in infants whose mothers have received iodine alone It is felt that the antithyroid drugs should be discontinued during the last month of pregnancy Thought should be given to the fact that during pregnancy the basal metabolism is normally elevated The administration of thiouracil preparations therefore in sufficient amounts to produce a lowering of the basal metabolic rate in a nonpregnant woman would *de facto* produce a degree of hypothyroidism during pregnancy The fear of producing hypothyroidism may be abolished if the antithyroid drugs are given for a short period of time only In this case report it is conceivable that the recurrence of the goiter in this infant at the age of 2 months might well have been due to the sulfonamides However the rapid regression of the thyroid enlargement forces one to assume that this is purely speculative [1]

Pregnancy

From January 1 1947 to December 31 1957 in a series of over 650 patients operated upon for thyroid disease only seven pregnant women with hyperthyroidism were encountered Five of these patients had primary hyperthyroidism and the other 2 had adenomatous goiter with secondary

would give more satisfactory results. A point to mention is that there is a great tendency toward keloid formation in children following thyroidectomy.

In children psychotherapy may be as essential a regimen as it is for adults. While confined to bed the child has games, toys and books which amuse him and keep him happy. When the child becomes ambulatory and returns home excitement and crying may become a problem. The cooperation of a child psychiatrist is often as important postoperatively as the preoperative preparation for thyroidectomy.

An interesting account on juvenile thyrotoxicosis was reported in the Journal of Pediatrics in 1954. Allen and his associates reported the therapeutic results obtained from 30 children in whom symptoms of thyrotoxicosis appeared before the age of 15. Fifteen patients received thyroid irradiation with or without stable iodine, and 15 others received prolonged treatment with the antithyroid compounds. In this latter group some received iodine and others did not receive it. These authors did not employ radioactive iodine in children with thyrotoxicosis, because they do not believe that the possibility of late untoward sequelae can be excluded in this form of therapy.[4] The final therapeutic results could be fairly well evaluated in 24 of the 30 children under treatment. A satisfactory remission of the toxic thyroid symptoms was obtained in 17 of these children. The results were similar in those who were irradiated and in those who received the antithyroid compounds. Five out of 6 children who were operated upon had a satisfactory remission of the disease following thyroidectomy. Allen and his associates feel, however, that thyrotoxic children without nodular goiters should be given a long trial with antithyroid medication before thyroidectomy is performed. They believe this in spite of the fact that the over all results from nonsurgical therapy do not compare as favorably as those results known to follow thyroidectomy. The preservation of an anatomically intact thyroid gland for the proper adjustment of the endocrine stresses of puberty and the remaining growth period plus the low incidence of post therapeutic myxedema are the major considerations which prompt them to pursue a conservative therapeutic regimen.[4]

Perlman of Canada presented an interesting situation in which a goiter developed in a premature infant.[175] The 26 year old mother of the infant whose case was presented by him had been taking 150 to 200 mg. of propyl thiouracil daily for one year. The dosage of this drug was increased on occasion to twice the amount for 3 or 4 days at a time. The month before delivery the patient increased the dosage of propylthiouracil to 300 mg per day. At the same time she was taking Lugol's iodine solution in amounts varying between 8 to 12 drops per day. The iodine was taken

Management of Hyperthyroidism during Pregnancy

Pregnancy leads to exacerbations of hyperthyroid symptoms so that the diagnosis is readily discerned. The major problem is of what therapy should be followed. Is medical treatment preferable to surgical intervention? It also is necessary what is the opportune time for thyroidectomy?

In the light of our previous discussion it appears that the prolonged use of the antithyroid drugs is not the method of choice. These drugs should not be used indiscriminately in the adenomatous type of gland with secondary hyperthyroidism. If necessary these drugs may be used in addition to Lugol's iodine as a preoperative regimen similar to the procedures followed in nonpregnant hyperthyroid patients. Thyroidectomy performed during the first half of pregnancy is the therapy of choice. Pregnant women tolerate thyroid operations very well and there is no indication for interrupting the pregnancy.



FIG. 34. Patient with moderately severe exophthalmic goiter (primary hyperthyroidism). Photograph illustrates markedly enlarged right and left lobes of thyroid gland. The thyroid isthmus is prominently visible.

Summary of Hyperthyroidism and Pregnancy

1. Pregnant women may develop hyperthyroidism or pregnancy may cause an overt manifestation of latent hyperthyroidism or an exacerbation of true hyperthyroidism during a period of recrudescence.

hyperthyroidism All 7 patients displayed marked toxic symptoms They were prepared for surgery and had an uneventful recovery

These patients were seen by more than one physician obstetrician and surgeon Surgery was advocated by some and advised against by others This was a source of great confusion to the patients In view of this confusion, it is appropriate at this point to reiterate certain facts in reference to the problem of hyperthyroidism and pregnancy

*As a preliminary statement it must be recalled that a moderate hyper*trophy of the thyroid gland occurs as a normal physiologic response to pregnancy This hypertrophy occurs (especially during the last trimester of pregnancy) in 65 to 90 per cent of women who become pregnant With or without thyroid hypertrophy there is a definite elevation in the B M P This rise is approximately +5 The elevation in B M R is more pronounced during the last half of pregnancy *Radioactive iodine should not be administered to a pregnant woman*

In view of our present knowledge of the effects of hyperthyroidism on the liver it is worthy to recall that during pregnancy the liver is in a state of imbalance If hyperthyroid stress is placed upon this disturbed equilibrium it is understandable that such a patient might easily develop those complications of pregnancy asociated with liver pathology Specific reference is made to eclampsia vomiting of pregnancy and acute yellow atrophy *of the liver This fact is an argument in favor of the urgency of proper* treatment of hyperthyroidism in pregnant women

Other contributions to our knowledge of the thyroid gland in pregnancy were made by Halsted and Ukita [110] The former demonstrated that partial thyroidectomy in pregnant dogs resulted in a marked hypertrophy of the gland in the offspring in order to compensate for the deficient maternal secretion Ukita showed that the removal of the thyroid gland from preg*nant rabbits prolonged labor and the baby rabbits were undersized poorly* developed and their thyroid glands were hypertrophied with evidence of increased ecretory activity The glands of the e pregnant animal were normal It has been proven that the enlargement of the thyroid gland seen in pregnancy is due to a true hyperplasia of the acinar structures and to the formation of new follicles In view of this hyperplasia it would be inadvisable to treat hyperthyroidism during pregnancy for a long period *of time with antithyroid drugs* because of the possibility of instituting carcinomatous changes In addition the prolonged use of an antithyroid drug may result in a goiter in the offspring If this does not occur the gland of the offspring is merely enlarged following the conventional use of the antithyroid drugs

fessed that the interrelationship of these disturbances cannot be explained fully at this time

A comparative study made by Buxton and Herrmann on 2 groups of euthyroid patients complaining of sterility and menstrual disorders revealed the following In an initial group of 339 patients only 131 could be considered for study These 131 patients were divided into Group A (75 patients) and Group B (56 patients)[1,5] The patients in Group A were treated empirically with thyroid extract Group B received only placebo tablets The thyroid activity of all patients was studied at regular intervals by means of the basal metabolic rate, protein bound iodine radioactive iodine uptake and serum cholesterol determinations It appeared to these investigators during this course of study that a single determination of any one of these laboratory tests especially the basal metabolic rate is not enough to evaluate thyroid function Moreover it is frequently misleading especially in the euthyroid patient

The information gathered revealed that the cure and improvement rates between Group A and Group B was not of much significance It was the impression of Buxton and Herrmann that the exogenous thyroid administered to their patients merely replaced the endogenous thyroxin that the thyroid gland would ordinarily produce were it not permitted to rest (or hibernate as it were) because of this outside assistance in maintaining its function Although this study by no means provides the final answer as to the efficacy of thyroid therapy in menstrual disturbances and sterility the failure to find any statistically significant difference in the results obtained in the two groups studied clearly indicates that the therapeutic value of thyroid administration for sterility and menstrual abnormalities is very questionable[3]

The Thyroid and Reproductive Function

Associated with the discussion on the relationship between the thyroid gland and the reproductive function Herring stated his opinion that the minor degrees of hypothyroidism may be practically symptomless and yet may seriously affect reproductive processes (J.A.M.A **113** 1300 1939)

This conclusion was reached following the study of 150 patients The discussion concerned itself with the causation of abortion and sterility in women This report showed that in an unselected group of 150 pregnant women the greatest number of abortions occurred in those whose thyroid activity was below the normal standard Inaccuracies might have occurred in this study since they based their diagnosis of hypothyroidism solely on the basal metabolic rate In 61 of the 150 patients studied

2 Under any circumstance the hyperthyroidism and not the pregnancy should be interrupted

3 Failure to interrupt the thyrotoxicosis may result in a spontaneous interruption of the pregnancy by nature herself

4 Hyperthyroidism in pregnant women is treated satisfactorily by surgery, after adequate preoperative preparation, without the fear of losing the fetus

5 When thyroidectomy is performed during the first half of pregnancy the patient usually goes on to a full term normal delivery

6 Prolonged treatment of a pregnant woman with an antithyroid drug may produce a goiter in the infant or stimulate carcinomatous changes in the gland of the mother

7 Whenever possible it is advisable to inform patients that pregnancy should not be undertaken for at least one year, and preferably two years after thyroidectomy

8 Radioactive iodine is contraindicated during pregnancy

Effect of Thyroid Therapy on Menstruation and Sterility

It is well to recall some current thoughts on the effects of the administration of thyroid extract on certain problems peculiar to women Thyroid therapy in the euthyroid obstetric and gynecologic patient has been open to much controversy during the past many years It is a common clinical impression of gynecologists that thyroid extract is of great value in the treatment of sterility and menstrual disturbance A contrary opinion is advanced by many internists, endocrinologists and thyroid specialists who offer much doubt concerning the efficacy of thyroid therapy for these conditions Buxton and Herrmann have studied this problem quite intensively [157]

These authors reviewed the literature and found that thyroid extract was administered for a multivarious group of gynecological disorder These disorders ranged from essential uterine hemorrhage amenorrhea and oligomenorrhea to sterility and menstrual disorders Actually there is no exact clear understanding of the relationship of the thyroid gland to the complicated mechanism of the pituitary gonadal endometrial axis As a matter of fact Buxton and Herrmann have shown that the evidence advanced in the literature is in truth contradictory Clinically speaking hypothyroidism as well as hyperthyroidism may be associated with every degree of menstrual disturbance from amenorrhea to acute metrorrhagia These menstrual symptoms may be due to anovulation and other ovarian underfunctions occurring in thyroid disorders It must be candidly con

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Thyroid Disease and the Climacterium

THE FINAL responsibility as to whether an operation is to be performed resides with the surgeon. It is his decision whether a thyroidectomy should be undertaken for the treatment of hyperthyroidism. The surgeon must know his patient thoroughly in order to treat hyperthyroidism. He cannot become a mere technician and leave the important field of diagnosis to other sources. Laxity in the proper knowledge of the patient's clinical background may result in a needless operation. In other situations thyroidectomy may eradicate mental symptoms and rehabilitate a person destined for a mental institution.

When a symptom complex is common to several clinical entities the possibility of confusion and error in diagnosis is understandable. Primary hyperthyroidism as a disease entity may present initial symptoms easily confused with other illnesses. This is especially true when psychomotor irritability is reflected in emotional complexes and sympathetic hyperactivity.

In middle life when physiologic dysfunction results from a diminution in activity of the glands supplying male or female hormones many symptoms are produced. The menopausal symptoms result from an imbalance of equilibrium between the sympathetic and parasympathetic nervous system. When this imbalance is associated with disturbances in the psychic brain centers clinical manifestations result which closely simulate primary hyperthyroidism. If in addition to these climacteric symptoms the patient happens to have a small or moderate sized thyroid gland an erroneous diagnosis of primary hyperthyroidism is easily made.

The frequency of symptoms elicited in hyperthyroidism and in the male and female menopause can be appreciated from a perusal of the accompanying table. Emotionalism, nervousness, irritability and excitability are symptoms of major importance in both climacteric and hyperthyroid patients. Often this grouping of complaints initiates the symptoms which bring the patient to seek medical attention. Not to arrive at a proper diagnosis at this time may result in improper management and therapeutic failure.

The sensation of warmth, hot flushes, intolerance to heat and free

hypothyroidism was demonstrated In this group there was a total of 21 miscarriages either in previous pregnancies or in the pregnancy during which these observations were made In contrast to this, the total number of all miscarriages in the normal and hyperthyroid groups together was only 9 From these results Herring concludes that the hypothyroid state is an important factor in the causation of fetal death and subsequent abortion and that this significance has not hitherto been sufficiently stressed

From the foregoing study of common symptoms it can be appreciated that confusion rather than assistance will result from a history alone. In the middle aged and menopausal group of patients the presenting symptoms closely parallel those noted in hyperthyroid individuals. Careful differential diagnosis, therefore, is especially important in this menopausal group.

The basal metabolic rate is not the *sine qua non* of diagnosis because many of the symptoms previously discussed would themselves produce an erroneous recording. When the basal metabolism has been elevated on the initial reading technical inaccuracies may be the cause. Repetition of the test each morning preceded by a small dose of a barbiturate will reward the observer with a normal reading.

When doubt as to the true underlying disease cannot be honestly eradicated, therapeutic tests are indicated. If borderline hyperthyroidism cannot be eliminated Lugol's iodine may be administered. Improvement under this medication will indicate hyperthyroidism. Radioactive iodine is a valuable diagnostic aid as well. Similarly when the symptomatology favors a diagnosis of the menopausal syndrome hormones may be administered. Alleviation of the patient's symptoms during the administration of estrogens or testosterone will establish the climacteric diagnosis.

Equally worthy of study is the activity of the thyroid gland in the menopausal patient. Usually cessation of ovarian hormonal activity does not directly alter thyroid function. However, a reflex effect on the thyroid gland through the pituitary gland may or may not occur. The master role of the pituitary on both ovarian and thyroid secretions is well known. Based upon this relationship thyroid hypofunction is allied to ovarian hypofunction during the climacterium. Clinically this has been observed in some women during the menopause. Often the robust woman at the time of her menopause will display certain features of thyroid insufficiency. She will gain weight but does not become obese. Her activities are diminished and are reflected in slowness of thought and action. Inability to keep awake, muscle fatigue and backache are frequent complaints. Other symptoms may be paresthesias of the hands, alopecia and dryness of the skin and hair.

This group of patients should be given thyroid extract in addition to the hormonal medications. Prior to administering thyroid extract a basal metabolic rate should be determined. The proper thyroid dosage is different for each patient. A satisfactory basal metabolic level is in the vicinity of −5 to −8 per cent. A suggested rapid method of raising the metabolic rate is to give 4 gr. of thyroid extract for 4 days, then reducing the amount to a maintenance dosage of 1½ gr. The basal metabolic rate should be checked once or twice weekly. When the basal metabolic level

perspiration are symptoms noted in both groups of patient Careful interrogation will readily separate this group of complaints into their proper category Hot flushes and the sensation of warmth are usually more marked during the menopause Intolerance to heat and facile perspiration are more pronounced in hyperthyroidism However, each of these symptoms is found in both hyperthyroidism and the climacterium



FIG 35 Primary hyperthyroidism with severe exophthalmos Acute exacerbation occurred during menopause This patient demonstrated the following eye signs widening of palpebral fissure (Dalrymple-Stellwag's sign) failure of upper lid to follow eyeball in its downward movement (Von Graefe's sign) weakness of convergence of both eyes (Moebius sign) and in addition absence of normal wrinkling of forehead (Geoffrey's sign) (Graham E A Surgical Diagnosis Philadelphia W B Saunders Co 1930)

Mental symptoms have been noted in both types of patient These symptoms may find expression as phobias and in advanced cases as true psychoses A series of hyperthyroid patients studied for the presence of a phobia was previously discussed [93] This study revealed many phobias of different types In menopausal patients the most frequent phobias are the fear of impending danger the fear of crowds and the fear of inadequacy This last fear finds its basis in the alteration of a previous full sex life Adequate questioning and physical examination will assist greatly in placing the patient in the hyperthyroid or climacteric group [101]

TABLE 4 *Group of Symptoms Common to Hyperthyroidism and the Climacterium*

Symptom	Hyperthyroidism	Female Climacterium	Male Climacterium
Nervousness	+	+	+
Menstrual disturbances	+	+	
Disturbed sleep	+−	+	+
Irritability	+	+	+
Excitability	+	+	+
Phobias	+	+	+
Hot flushes (sensation of warmth)	+	++	+
Intolerance to heat	+	+	+
Palpitation	+	+	+
Emotionalism (crying)	+	+	+
Free perspiration	+	+	+
Psychoses	+	+	+

Thyroid Surgery in the Elderly

The usual clinical features of thyroid disease may be absent in the elderly patient. Even in aged persons with hyperthyroidism the effects of excessive thyroid activity are less pronounced than in the younger adult. Although fortunately hyperthyroidism is infrequent among the elderly, thyroid surgery has a place in the treatment of the aged patient.

Indications for surgical treatment are:

1. Apathetic hyperthyroidism
2. Thyrocardiac disease
3. Tracheal compression secondary to adenomatous goiter
4. Cancer in the thyroid gland

1. Excessive hyperthyroidism in the aged may present itself as apathetic hyperthyroidism. This term describes the elderly patient with toxic hyperthyroidism who does not have exophthalmos, tremor and the other signs of hyperthyroidism. On the contrary, they have an indifferent or apathetic facies which beguiles the true underlying disease. These patients do have tachycardia and cardiac arrhythmias. Many of these individuals' signs are unrecognized and are treated as heart cases.

2. Hyperthyroid heart disease or thyrocardiac disease in the aged is seen by the surgeon as often as the internist. Apathetic hyperthyroidism is seen rarely by both surgeon and internist. Internists are alert to the presence of this etiological type of heart disease and make the correct diagnosis in almost all instances. The patient, in spite of his age, is rapidly prepared for surgery and with adequate surgery excellent beneficial effects on the patient result. The internist is often able to control this type of cardiac patient with great ease following thyroidectomy.

is then established, the maintenance do age may be modified if it becomes necessary to do so It may take one month to establi h a maintenance dose by this method Thyroid extract may be given for a period of 4 to 6 months

The preferable method is to raise the metabolic rate slowly Small do es of thyroid extract (½ gr to 1 gr) may be administered for 1 or 2 weeks Following an interval of 2 to 3 weeks the dosage may be further increased Associated with an elevation in the basal metabolic rate the patient be comes subjectively improved The patient can be maintained with 1 or 2 grains of desiccated thyroid daily for 4 to 6 months

Menopause and Hyperthyroidism

During the menopause the truism that 'once a hyperthyroid always a hyperthyroid is recalled The close harmonious linkage between the pituitary gland as the master regulator the thyroid and the ovaries is distorted during the menopau e This discord results in many symptoms often difficult to separate into their proper clinical category Frequently the menopause is as ociated with an acute exacerbation of thyroid symp toms in a patient who has had a thyroidectomy for hyperthyroidism These patients should be given iodine during the period of treatment for meno pausal complaints Another type of patient develops hypothyroidi m with the onset of the menopause The rational administration of thyroid extract alleviates the hypothyroid picture These facts stre s the phys iologic role of the thyroid gland during the climacterium For this reason during the menopause special observation and consideration should be given to the post thyroidectomy patient as well as to other individuals with a previous thyroid history The reason for this consideration is the fact that many menopausal symptoms can be attributed to thyroid activity

Treatment of the thyroid dysfunction will alleviate many of the com plaints attributed to the climacterium This is especially true in tho e individuals who are not respon ive to a prescribed rational therapeutic regimen for the control of the menopau al syndrome These individuals may have an underlying thyroid state which when treated in conjunction with hormonal therapy will produce remarkable clinical improvement

Often the similarity of complaints in the hyperthyroid and menopau al patient camouflages the underlying disease This may result in erroneous treatment Responsibility rests upon the surgeon He must separate the climacteric individual from the true hyperthyroid patient His watchful ness and final decision will prevent a thyroidectomy on a menopau al patient, even as he can erase many symptoms previou ly mentioned from those with true hyperthyroidism

9

Thyroiditis

Struma Lymphomatosa

DISORDERS OF the thyroid gland have fascinated surgeons since 1878 when Theodore Kocher first published his report of a successful thyroidectomy [9] Accentuated interest in this subject found an impetus in 1912 when Hashimoto described a new pathologic entity in the thyroid gland Since he was the first to describe the lesion it bears his name as well as the descriptive term struma lymphomatosa or lymphoid goiter [9]

This clinicopathologic entity is unusual because of its low incidence as well as its bizarre pathologic picture and symptom complex A study of the literature will show many discrepancies as to the exact number of cases reported since it was first described by Hashimoto In order to clarify this problem A Graham in 1931 studied the literature extensively [4] He divided the reported cases into ten categories interpreting and grouping them for statistical purposes His analysis clearly demonstrated the existing confusion duplication and lack of proper identification in the various cases reported For this reason no accurate determination of the number of cases of struma lymphomatosa is possible However up to the present time various authors have reported small series of cases Thus it can be appreciated that this entity is infrequently encountered during the professional career of the average surgeon

Etiology and Pathology

The exact causative factor in the production of struma lymphomatosa is unknown It has been suggested that exhaustive atrophy is a recognized change in Hashimoto struma and that this degeneration might be associated with some form of compensatory hyperplasia resulting in this disease Graham s study has led him to express the opinion that there is no proof that hyperthyroidism hypothyroidism suppuration tuberculosis syphilis or neoplasm are factors in the causation of struma lymphomatosa Although the exact nature of the condition has not been determined the current belief is that Hashimoto s disease should be included in the same category with Riedel s struma Although frequently confused with Riedel s struma many authors have concurred in the opinion that Riedel s struma and Hashimoto s disease are two distinct pathologic entities

3 An indication for surgical intervention in the aged thyroid patient is tracheal compression secondary to adenomatous goiter Situations of this type were seen in ten elderly patients, all over 65, who presented a similar history of having a pre existing goiter which suddenly increased in size Associated with the sudden enlargement was ' wheezing respiration and respiratory distress when lying flat in bed The sudden thyroid enlargement is attributed to hemorrhage in a cystic adenoma The hemorrhage arises from a rupture of an arteriosclerotic vessel in the adenomatous structure

4 Elderly thyroid patients may be subjected to thyroid surgery for another reason namely carcinoma In years gone by, the outlook for a patient with thyroid cancer was disheartening Modern surgery, radioactive iodine and radiation therapy bring new hope to such victims Elderly patients with advanced cancer are no longer given passive nursing care Active treatment is now available, and when employed to its utmost can prolong the life of those who are advancing in years

In the management of thyroid cancer the surgeon can perform an almost total thyroidectomy This thyroidectomy may or may not be associated with a radical neck dissection on one or both sides of the neck Following surgery radiation therapy with or without the administration of radioactive iodine is a valuable supplement to the surgical procedure Combined treatment of this kind has benefited many patients afflicted with thyroid cancer

enclo ed in the connective ti ue It is areas of this type which often lead to the erroneous belief that Ha himoto s di ea e is an early stage of Riedel struma Micro copic study of the blood ve els reveals no remarkable al teration in their normal architecture except for the fact that an abundance of round cell infiltration is noted around the larger ve el

Thus truma lymphomato a i a lymphoid goiter characterized by a growth of lymphatic element in the formation of lymphoid follicles to gether with certain changes both in the parenchyma and in the inter titial ti ue of the thyroid gland

TABLE 5 *Differentiation of Hashimoto s Disease and Riedel s Struma*

H hm t s D se se	R ed l Strum
It is practically always confined to women	Di ea e is reported equally in men and women
A history of myxedema may be ob tained	There is little tendency toward myxedema e pecially following an operation
Glandular involvement is diffu e and bilateral	Involvement is usually unilateral follow ing a di crete nodule
Pres ure symptoms are of the tracheal constricting variety	Pre ure ymptoms such as hoar ene s difficulty in swallowing and limitation of the cord on the involved ide are common
Periglandular adhe ions are ab ent	Pronounced adhesions to adjacent struc tures are found
Pyramidal lobe is prominent	Pyramidal lobe is u ually not promin nt
Histologically fibro is is circum cribed	Histologically fibrosis is diffuse
Lymphoid hyperplasia is pronounced	There is no lymphoid hyperplasia
There are larg lymph follicles present	Giant cells can be identified in the fibrous ti sue

Clinical Picture

The di ease almost always occurs in women It has an in idious on et and follow a chronic cour e The duration of symptoms may vary from 9 months to 5 years or more The clinical manifestations result from pres ure of the hardened gland on the trachea Usually there are no recent symptoms of a disturbed thyroid function in patients having the disease for a long period When the di ease i of a chronic nature however there is almo t always an a ociated hypothyroidi m at one time or another in the patient s pa t hi tory The basal metabolic rate is usually within normal limits On occ i ion the ba al metaboli m may be below normal Infre quently evidence of mild myxedema may be noted

A cla ic clinical history of struma lymphomato a may be given as fol lows The patient is a 40 year old woman who for many years has had en

Micropathologic study of this disease reveals a dense diffuse lymphoid infiltration between the follicles with occasional formation of secondary nodules Sometimes these follicles are extremely prominent, so that the microscopic picture may closely simulate a lymph node Hence the terminology struma lymphomatosa or, as it is sometimes called lymphomatoid or lymphoid goiter There tends to be a variation in the intensity of the lymphocytic infiltration from occasional scattered lymphocyte among colloid containing follicles or even absence of infiltration in certain

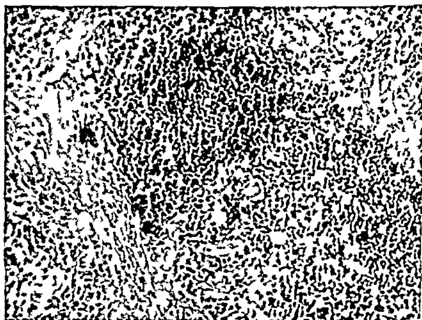


FIG 36 Photomicrograph (170×) of histologic section of struma lymphomatosa This low power view shows typical lymphocytic infiltration of the thyroid gland with a tendency toward formation of a structure simulating a lymph node

areas, to complete displacement of the normal thyroid with confluent masses of lymphocytes forming secondary nodules Other types of cells found are monocytes and occasionally plasmocytes Notwithstanding the abundance of lymphocytic infiltration the lymphoid tissue does not demonstrate a definite formation of lymph node That is there is no formation of sinuses

The connective tissue is usually swollen poorly stained and the cells have few nuclei Mononuclear lymphocytes may be readily identified in *the connective tissue* In rare instances the interlobular and intralobular connective tissue may be sufficiently increased to predominate over the lymphocytic infiltration When this occurs small islands of follicles are

produces a soft gland and does not possess the physical characteristics of struma lymphomatosa. Calcified adenoma, either solitary or multiple, are readily identified by calcific roentgenographic evidence of this type of degeneration.

Struma lymphomatosa on occasion may be difficult to differentiate from neoplastic lesions. However, it may be distinguished from malignant disease by the following points:

1. In struma lymphomatosa all areas of the gland are involved without serious encroachment on tissue outside the thyroid gland.
2. Neoplasm involves all areas including the main vessels and nerves.
3. Struma lymphomatosa does not produce an irregular nodular surface of the gland.
4. Regional glandular enlargement due to metastases is absent in struma lymphomatosa and is usually prominent in neoplasms.

Whenever a satisfactory differentiation between carcinoma of the thyroid and struma lymphomatosa is not possible, pathologic study of the operative specimen will decide the question.

The present tendency among pathologists and surgeons is to regard struma lymphomatosa and Riedel's struma as distinct diseases.[9] Often these entities are difficult to differentiate from each other. For this reason the foregoing table is significantly valuable. In addition to the points given, Riedel's struma may be "frozen" in the neck. It is the hardest pathologic entity (except a calcified adenoma) felt in the neck. It is as hard as cartilage and cuts with difficulty. Hence it has been called variously "iron struma," "ligneous" or "woody" thyroiditis.

Treatment

Operation in struma lymphomatosa is indicated for two reasons: 1. to differentiate the lesion from cancer; 2. to relieve or prevent pressure symptoms. At the time of operation the true identity of the pathologic change in the thyroid is revealed. The gland with Hashimoto's disease is enlarged from 2 to 5 times the normal size. It is not adherent to adjacent structures. Thus it is immediately differentiated from cancer or Riedel's struma. The gland is gray pink in color and firm in consistency. When sectioned it is white with a suggestion of focal edema. Compression of the gland with a clamp results in the extrusion of a serous fluid. Clamps grasp the tissue poorly and hold fast only to the fibrous capsule and blood vessels in the gland parenchyma. Bleeding is not remarkable because of compression and at times complete occlusion of blood vessels. This occlusion results from an increased fibrofollicular pressure which is characteristic of Hashimoto's disease.

The surgical procedure is a routine subtotal thyroidectomy. However,

largement of the thyroid, which grew rather slowly She complains of weakness fatigability slight nervousness and some pressure symptoms The pressure symptoms may be described as hoarseness choking or dysphagia On occasion a brassy cough or a roughening of the voice may be noted

The gland with Hashimoto s disease will unfold the following diagnostic criteria

1 The gland has a diffuse pebbly feel
2 It feels as hard as exophthalmic goiter with iodine involution
3 The superior poles are extremely broad being broader than the poles of primary hyperthyroidism
4 The pyramidal lobe is enlarged similar to the enlargement of the lobe in primary hyperthyroidism

By seeking to determine the presence of these criteria, one can make the preoperative diagnosis of struma lymphomatosa with accuracy in most instances

Diagnosis

The most valuable clinical aids in arriving at a diagnosis of struma lymphomatosa are obtaining an adequate history and performing a satisfactory examination of the thyroid gland If the signs and symptoms parallel the clinical picture previously presented a tentative diagnosis of *struma lymphomatosa can be made*

Struma lymphomatosa must be especially differentiated from other chronic infections and neoplasms of the thyroid gland The most confusing lesions are

1 Chronic nonspecific thyroiditis
2 Chronic specific thyroiditis
   a Tuberculosis
   b Syphilis
   c Actinomycosis
3 Calcified adenomatous goiter
4 Lymphosarcoma
5 Carcinoma
6 Riedel s struma
7 De Quervain s disease

Nonspecific *thyroiditis is eliminated immediately in arriving at a diagnosis* since Hashimoto s disease displays the absence of acute inflammatory symptoms Hashimoto s disease is bilateral may be associated with hypothyroidism, and does not have a tendency toward spontaneous cure Specific granulomatous lesions are differentiated by the absence of any specific evidence of the causative organisms of tuberculosis syphilis or actinomycosis The enlargement of the thyroid gland in specific infections usually

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The surgical procedure is a routine subtotal thyroidectomy However,

the operation is less radical than that for primary hyperthyroidism The remnants of the thyroid are sutured to the trachea in such a way that the midline of the trachea is free of thyroid tissue By the prevention of contiguity of the remnants of the thyroid the possibility of future tracheal compression is avoided

Recurrent compression of the trachea may result following thyroidectomy This recurrence is occasioned by a contraction of scar tissue which



Fig 37 Microscopic section illustrating an important point in the histologic differentiation of Riedel's struma from Hashimoto's struma In Riedel's struma there is a persistence of normal colloid in some acini as shown here The fibroblastic reaction which precedes and accompanies the fibrotic process may be confused with spindle cell sarcoma (Price I W Histology of the thyroid gland Medicine Illustrated Feb 1949)

has replaced the removed thyroid glandular elements When this situation occurs the tracheal compression may be sufficient enough to diminish the size of the trachea With this diminution in size there may be an interference with the respiratory quotient of the lungs A second surgical procedure is rarely necessary for thyroiditis Occasionally when severe tracheal constriction results from excessive scar tissue formation, surgical correction may become necessary When this situation is encountered further constriction can be avoided by suturing the prethyroid muscle to the trachea over any remaining thyroid tissue on either side of the trachea This will prevent in most cases, the formation of any scar tissue from developing between the musculotracheal suture site in the future



Fig 38 Gross specimen of the thyroid gland (cross section of a lobe) showing the dense white appearance of Riedel's struma with central liquefaction and cyst formation (Price L W Histology of the thyroid gland Medicine Illustrated Feb 1949)



Fig 39 Riedel's struma showing dense fibrosis of the capsule with extension into adjacent muscle tissue Barr D P Thyroiditis and myxedema Bull New York Acad Med July 1953)

The postoperative course is usually uncomplicated Brawny thickening of the cutaneous layers may occur, and may persist for many weeks In most instances myxedema can be anticipated Patients should be advised of this possibility prior to operation Patients are followed postoperatively with routine determinations of the basal metabolic rate the cholesterol level, and protein bound iodine for this reason Control of the myxedema is not difficult with a daily dose of thyroid extract After operation, these patients are much relieved and are considered well as soon as the myxedema is controlled There have been no reported instances of recurrence of the disease following thyroidectomy Operative mortality does not differ from the mortality in routine subtotal thyroidectomies

Prognosis

Untreated struma lymphomatosa may pass into myxedema After thyroidectomy, complete and permanent relief of pressure symptoms results although the onset of hypothyroidism may be accelerated If this condition is anticipated, the postoperative administration of thyroid extract should be commenced as soon as incipient myxedema is suspected

Postoperative recurrence is unusual So called recurrence can be attributed to inadequate surgical treatment This occurs if the bilateral nature of the disease is not recognized and results in a unilateral re ection which fails to adequately relieve the pressure symptoms It is a mistake to assume that the disease has in the interval merely spread from one lateral lobe to the other for which view there is no reliable evidence The explanation is most probably that in certain asymmetrical goiters (based on congenital asymmetry of the thyroid gland) one large lateral lobe may so overshadow the other small lobe that the latter is allowed to remain undisturbed "[9]

Résumé on Hashimoto's Disease

Many studies have indicated that Hashimoto s disea e is listed among the rarer surgical entities The salient feature of this disease is that its exact causation is unknown It occurs almost entirely in women in the third fourth and fifth decades of life The fundamental pathologic change is a lymphocytic infiltration associated with follicular pressure atrophy Vascular channels are obstructed because of fibrofollicular pres ure Clinically the most important findings are demonstrated by palpation of the thyroid gland The features of struma lymphomatosa are broadening and enlargement of the superior poles and hard firm lobes giving the impression of a pebbly surface Enlargement of the pyramidal lobe as in hyperthyroidism is notable Pressure symptoms may or may not be present

Surgical treatment is indicated to relieve pressure symptoms and to differentiate the disease from neoplasm

Little is known at present as to the course of untreated Hashimoto's disease since patients in all the reported cases have been subjected to operation or radiation therapy Thyroidectomy will relieve pressure and nervous symptoms If postoperative myxedema occurs, it can be counteracted by the administration of thyroid extract

De Quervain's Disease

Any discussion on thyroiditis would be deficient without some mention of De Quervain s disease Clinically De Quervain s thyroiditis does not simulate Riedel s struma It may however, occasionally resemble Hashimoto s disease when fever pain and thyroid tenderness are present in struma lymphomatosa

The composite clinical picture of De Quervain s disease is as follows

1 It is most common in women (of any age)
2 It has an acute febrile onset
3 Fever leukocytosis and a rapid sedimentation rate are common
4 The thyroid gland is tender to palpation
5 Pain in the gland is referred to the ears and mandible
6 The thyroid gland may enlarge bilaterally to twice its normal size
7 The duration of the disease is from several days to several weeks
8 It is a self limited disease with recovery the usual end result
9 A small uptake of radioactive iodine is usual with a greater than normal urinary excretion of I^{131}

It is interesting to note that the response of De Quervain s disease to radioactive iodine is similar to that observed in advanced myxedema although the patients exhibit none of the clinical manifestations of hypothyroidism [1 5 1 6] Contrariwise during the active stages some symptoms and signs suggest thyrotoxicosis [119 1 1 1] Hence radioactive iodine is of value in the differential diagnosis between primary hyperthyroidism and De Quervain s disease

The pathologic changes in De Quervain s disease are quite different from Riedel s struma and Hashimoto s disease Pathologic material for study of this interesting inflammatory thyroid lesion has not been frequently available and is not easily obtained Thirty two years elapsed between De Quervain s first and second publications [1 0 1 1] During these years he was able to examine only 8 new cases and from the reports of others he could identify only 62 case

Pathologically in the early active stages of the disease large areas of the thyroid gland show a destructive process The acinar cells of the thy

roid follicles disappear and their former location is recognizable only by the persistence of residual colloid after partial spillage into the surrounding tissue spaces Around the former acini there are numerous extremely large



Fig 40 De Quervain s thyroiditis exhibiting extensive destruction of thyroid acini and numerous multinucleated giant cell (Barr D P Thyroiditis and myxedema Bull New York Acad Med July 1953)



Fig 41 High power view of De Quervain s thyroiditis showing the relation of the multinuclear cells to the surrounding tissue (Barr D P Thyroiditis and myxedema Bull New York Acad Med July 1953)

multinuclear cells These apparently have phagocytized the colloid and constitute the most distinctive and diagnostic feature of the disease

During the acute phase there may be considerable infiltration with lymphocytes plasma cells and polymorphonuclear leukocytes Small abscesses have been observed at different stages of the disease As the disease

progre   es marked fibrous ti sue reaction occurs which is o marked that De Quervain s disease may be reported by the pathologist as Riedel s struma



Fig 4 Photomicrograph of an operative thyroid specimen removed from a 39 year old housewife who e major complaint was tracheal constriction At the time of operation the gro s appearance of the gland sugge ted struma lymphomato a The histologic picture is that of De Quervain s disease It is intere ting to note that the pathologi t described this section originally as Riedel s struma and later altered hi opinion in favor of De Quervain s disea e

The Reticuloses

Certain diseases of other endocrine glands besides the lymphoid system, may alter the architecture of the thyroid gland This is e pecially noted in Mikulicz s disease which involves the alivary and lacrimal glands The lymphoid hyperpla ia that occur in the submandibular and lacrimal glands may appear in the thyroid gland as well Thus it must be remembered that a patient with Mikulicz s di ease may have an associated lymphoid hyperplasia of the thyroid gland

When sarcoidosis is generalized a hypertrophy of the thyroid gland may occur Microscopic examination demonstrates a diffuse lymphoid infiltration in the thyroid gland Clinically the thyroid gland may or may not be enlarged

Sjogrens di ease is similar to lymphoid hyperpla ia of the thyroid gland

The presence of this disease may alter the histological picture of the thyroid gland in some individuals The same statement may be made in reference to lymphosarcoma Apropos of this statement Levitt writes "I studied a patient who displayed the clinical characteristics of so called Hashimoto s disease She eventually died and the autopsy revealed lymphosarcoma Lymphosarcoma could be differentiated from early fibrolymphoid hyperplasia of Hashimoto by the relative absence of extrathyroid involvement in the latter In the earlier stages of lymphosarcoma, however the thyroid does not manifest characteristic surface changes or fixation The rapidly lethal course of lymphosarcoma soon proves the diagnosis"[14]

Treatment of Nonsuppurative Thyroiditis

The increasing frequency of acute thyroiditis subsequent to upper respiratory infections and as a manifestation of systemic infection, has enabled the clinician to arrive at an efficacious method of therapy In the past many drugs have been employed to counteract thyroiditis Among these were the sulfonamides the antithyroid drugs and more recently the antibiotics It has been found that the best mode of therapy for acute thyroiditis of nonspecific and nonsuppurative type is to administer the steroids A regimen of exceptional value is to give the patient 80 mg of ACTH intramuscularly for 3 days Following the parenteral route cortisone is prescribed for oral administration It is given in 25 mg tablets every 6 hours for 2 days then every 8 hours for the third and fourth days and finally every 12 hours for the final 2 days After this course of therapy the thyroid gland returns to normal An indication that the inflammation has disappeared is the absence of pain on palpation and the disappearance of any glandular enlargement The use of ACTH and cortisone as just outlined is as of now the most satisfactory method of treating nonsuppurative acute or subacute thyroiditis

Hurthle Cell Adenoma of the Thyroid

The Hurthle cell tumor is among the surgical pathologic entities encountered in thyroid surgery and one of the rarer adenomata seen in the thyroid gland

Hurthle in 1894, described a large oxyphilic parafollicular thyroid cell as part of the normal thyroid gland[397] Langhans described the same cell in tumors of the thyroid Later these cells were found in association with adenomas and adenocarcinomas of the thyroid and have since been known as Hurthle cell tumors The origin of the Hurthle cell tumor has not been defined explicitly[349] Wilensky and Kaufman have discussed in detail the histogenesis of the Hurthle cell Suffice it to say that the Hurthle cell ha

been traced to several different origins by various writers Eisenberg and Wallerstein believed that the tumors were of parathyroid origin[349] Getzowa claimed that the Hurthle cell came from ultimobranchial bodies[394] Others as pointed out by Wilensky and Kaufman, believed that the

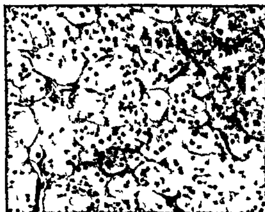


Fig 43 Low power histologic section showing Hurthle cell adenoma of the thyroid gland The characteristic histologic features are trabeculae and the large vacuolated cells



Fig 44 Microscopic section showing carcinoma which has developed in a Hurthle cell adenoma *This section resembles the benign adenoma in appearance but close ob*servation shows mitotic activity Local infiltration of adjacent tissues was present in addition to the mitoses (Rice L W Histology of the thyroid gland Medicine Illustrated Feb 1949)

Hurthle cell is a phase in the development of thyroid epithelium. As such it would not represent a distinct anatomical unit but rather a functional change, probably nutritive.

Therefore the derivation of this tumor is obscure. It has been stated that the cell of origin is a thyroid unit, other opinions have maintained that it is a parathyroid derivative. Some believe it to be a stage in the secretory phase of the thyroid epithelium. There are others who state that this type of adenoma is a product of degeneration. According to Symmers, the tumor arising from this cell is divisible into two varieties: (1) an adenoma showing no malignant qualities and (2) a tumor displaying the ability to metastasize, thus falling into the category of a malignant neoplasm.[116] In a consecutive series of 500 thyroid procedures only one instance of Hurthle cell tumor was encountered by the author.

Case Report. The patient was a 47 year old business executive who was seen for the first time in August 1951. He presented the history of an enlargement in the right side of the neck over a two month period. No toxic symptoms were reported. The significant physical findings were found in the right side of the neck where a visible mass was noted. This mass was partially subclavicular in location and moved with deglutition. The preoperative diagnosis of a right cystic adenoma was made. The patient was prepared for surgery and operated upon. A right hemithyroidectomy was performed without any operative or postoperative complication.

Pathology Report. The surgical specimen was that of thyroid gland measuring 6 by 3.5 cm. It was largely made up of a well-encapsulated nodule, the cut surfaces of which were amber and dark red. A rim of normal thyroid tissue surrounded the nodule.

Microscopic study indicated that the nodule had a connective tissue capsule from which vascularized trabeculae penetrated into various directions dividing the tumor into lobules of various sizes and shapes. The cells were roughly polygonal in shape with an alveolar like formation. These cells were large and pale in type. The cytoplasm was eosinophilic containing small oval deeply staining nuclei. The pathologist's diagnosis was Hurthle cell adenoma.

Comment. It was thought that the adenoma here reported was not malignant. However, it was further thought that Hurthle cell adenoma should be considered similar to other adenomata of the thyroid in regard to malignancy. Since it is the consensus of opinion among thyroid surgeons that 7 to 8 per cent of thyroid adenomata are potentially malignant, this concept should also be applied to the thyroid adenoma under discussion. However, the Hurthle adenoma is so rarely encountered that it is doubted that an adequate series is available to determine the percentage of malignant adenomata in a stated number of cases.

There is a Hurthle cell tumor described which is congenital in origin. The cell derivation of this congenital adenoma, as in the adult type, is not definitely established. It may find its origin in the thyroid, the parathyroid or another glandular structure. It is mentioned here for completeness of the available existing information on this subject.

10

Thyroid Crisis

FORTUNATELY THE modern surgeon does not encounter thyroid crisis as often as surgeons did several decades ago. In truth it may be said that many present day surgeons may not witness a complication of this type during their entire professional career. This diminution in the occurrence of thyroid crisis may be attributed to the following:

1. Excellent preoperative evaluation of the patient considered for thyroidectomy.
2. Adequate preoperative preparation of the individual to undergo surgery.
3. The proper administration of the antithyroid drugs.

Although many surgeons complete their surgical training without ever having observed thyroid crisis (thyroid storm), this condition nevertheless is always a possibility and should be anticipated. It is particularly more probable in patients with an initial basal metabolic rate between +80 and 100. Surgery should not be attempted on a toxic thyroid patient until the weight is increasing and the pulse rate is either near normal or is maintained at a steady level. Attention should also be given to the fact that nervousness and emotional instability must be under control and that the pulse rate is near normal and that the metabolic rate is +20 or below. Even when these criteria are fulfilled the possibility of a thyroid crisis following surgery must be considered. One must also remember that thyroid storms may be a preoperative complication as well as a postoperative one. The most efficacious treatment of postoperative thyroid crisis is to avoid this complication if it is at all possible.

Zondek was the first to describe hyperthyroid crisis and coma.[1] He stated that this syndrome is characterized by marked motor restlessness with uncoordinated movements of the entire body associated with a rapid *rise in temperature* and a lack of reactivity on the part of the patient. Increased obnubilation may lead to a syndrome which resembles catalepsy or bulbar paralysis.

The clinical picture of thyroid storm according to Means is that of a fulminating increase in the symptoms of thyrotoxicosis. The pulse may rise to 200. The patient is very irritable, often delirious, and at the same time weak to the point of collapse. Coma may supervene and death occur. A prominent feature of storm is hyperpyrexia. In contrast to the usual

preservation of heat in the presence of heightened metabolism in thyrotoxicosis the mechanism breaks down and the temperature rapidly ascends to between 100 and 106 F or more during crisis It is to be looked upon as in the hyperpyrexia of sunstroke, as due to toxic destruction of the body's organization for eliminating heat The entire course of thyroid crisis, from the initial symptom to death, may only be a few hour Recovery is possible, but not the rule

Lahey called attention to the early signs of an impending crisis[3] *These* are

1 A persistently unexplained increase in pulse rate is a definite indication of a threatening thyroid crisis
2 When a thyroid patient begins to show vague, transient but definite periods of irrationality an impending crisis may be in evidence
3 Vomiting may be another prodromal sign This indicates the inability of the individual to take in fluids and food and thus to combat the effects of the increased combustion associated with thyroid disease
4 A patient with a definite diarrhea likewise becomes a candidate for a crisis because even though fluid and food be taken, they are rapidly lost as a result of the diarrhea The metabolic balance is not maintained hyperthyroidism becomes intensified and the danger of a crisis is imminent

Crile Jr summarized this state A thyroid crisis is a vicious circle of hyperthermia and hypermetabolism With each degree of elevation of temperature, there is an increase of +12 per cent in the B M R and with each increase in the rate of metabolism there is a proportionate increase in the production of heat by the body "[4] Under these circumstances the patient burns up his tissues until he is exhausted

Theories of Thyroid Crisis

As in many problems associated with the physiodynamics of disease the exact cause of thyroid crisis is unknown With this uncertainty no general agreement as to etiology can be postulated This has resulted in many theories according to the experience of investigators who have studied this entity

Herget in 1940, reviewed the various theories promulgated by Europeans There was among the eccentric theories quoted one by Just This author stated that the rise in temperature (in crisis) is due to operative trauma in that disintegration of proteins takes place and leads to irritation of the heat center Hergot further reveals that many authors up to

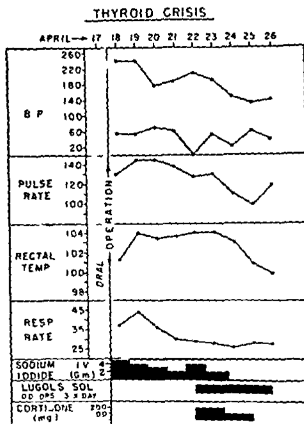


FIG 45 Clinical chart of a 44 year old Negro female who developed a postoperative thyroid crisis This patient was treated preoperatively with iodothiouracil (combination of iodine and thiouracil) She was given mercaptoimidazole irregularly from July 28 1950 to September 1951 On September 21 1951 she was given iodothiouracil (100 mg t.i.d dose increased later) The B M.R was +25 in April 1952 when she was admitted for surgery On April 18 1952 a subtotal thyroidectomy was performed The above chart shows the temperature pulse respiration and blood pressure changes during the immediate postoperative days This patient was treated with cortisone intravenous glucose plus sodium iodide vitamins sodium amytal sedation and oxygen In addition the hyperpyrexia was combatted by means of salicylate cold packs ice water enemata cooling fans and antibiotics The patient was discharged from the hospital 14 days after operation Patient of Seven and Perloff [*]

the writing of his article believed that crisis is due to postoperative hyper thyroxemia This hyperthyroxemia may be provoked by many factor Among the provocative causes he mentioned are

1 Operative manipulation of the thyroid gland which mechanically increases thyroxine in the blood and

2 Reflex influence on the hormonal secretion by injury to adjacent nerves

Bier (quoted by Herget) assumed that hyperthyroid coma actually constitutes a hypothyroxemic shock due to lack of active thyroid hormone Sauerbruch (quoted by Herget) attributes crisis to a sudden reduction in the hormone concentration after subtotal resection This leads to a disturbance of endocrine and nervous equilibrium producing postoperative crisis Kappis (quoted by Herget) stressed a shift in the ionic equilibrium toward the acid side as a participating factor in the causation of crisis

The thymus has been accused as the etiological agent in crisis by Kocher (quoted by Herget) He observed thymic hyperplasia in more than 50 per cent of deaths from Basedow s disease Garre and Borchard elaborated upon this thought by stating that it is produced in patients with a persistent thymus This gland acts on the heart and produces an increase in the effect of thyroid secretions Garre (quoted by Herget) was able to cure patients with Basedow s disease by extirpation of the thymus Foss and associates studied this problem and concluded that while so called thymic death does not resemble in many respects death from thyroid crisis the majority of patients dying in crisis will be found, at autopsy to have a persistent and hypertrophied thymus "[6]

Herget likened crisis to an allergic or anaphylactic reaction He believes that crisis might be prevented in the same way as the anaphylactic shock of serotherapy might, and can be avoided by preliminary injection of a small desensitizing quantity of serum

McGregor thought that an underlying polyglandular stimulation in certain adolescents resistant to iodine was a factor[7] Thus he stressed preoperative radiation of the pituitary and adrenal glands with satisfactory results In keeping with this endocrine concept Nash called attention to the antuitary[8] He maintained that thyroidectomy causes the antuitary to produce an increase of thyrotrophic hormone besides other hormones This postoperative outpouring of potent antuitary substances may induce the so called thyroid crisis 'one or more of the hormones having probably a greater influence in this direction than the others

Further thoughts on the relation of the thyroid gland to other glands attracted interest to the adrenal Levy was the first investigator to demonstrate that injections of adrenalin caused an action current in the thyroid gland[9] In addition, he pointed out that thyroid secretion renders the sympathetic nerve endings more excitable when acted upon by adrenalin It had further been revealed that as a result of the administration of adrenalin glycosuria in animals disappeared after excision of the thyroid The

glycosuria reappeared however when the animal was fed thyroid extract There is known to be a reciprocal inhibition between the thyroid and the pancreas on the one hand and between the pancreas and chromaffin system on the other[10]

The adrenalin test of Goetsch[11] was based on the work of Levy who showed that in hyperthyroid disease the sympathetic nerve endings were abnormally sensitive to small doses of adrenalin Further evidence to support the adrenal thyroid relationship was found by Goetsch and Ritzmann[1] Hyperadrenalism whether due to psychic influences anoxemia or other causes may exert some influence in the precipitation of thyroid crisis Prevention therefore of both disturbing stimuli and anoxemia is essential to the well being of the thyrotoxic patient The evidence offered by Goetsch and Ritzmann indicated that adrenalin should not be given in thyrotoxicosis[13] Additional studies by Maddock and his associates[14] increased the evidence in favor of the adrenal theory Substantiating the relationship between the adrenals and thyroid crisis Rea employed spinal anesthesia in the treatment of thyroid crisis[1] This procedure was offered on the basis that spinal anesthesia temporarily denervates the adrenal glands The observations by Brice and Reid brought forth additional clinical evidence regarding the ergotoxine ergotamine adrenalin relationship[16]

In 1936 Lahey reiterated the hypothesis that hyperthyroidism was allied to hyperiodinism[1] The work of the Lahey Clinic chemist Perkin on blood iodine and its relation to toxic thyroid states is widely known He found that in normal individuals thyroxine is confined to the thyroid gland whereas in toxic states increased thyroxine is found circulating in the blood The low amount of iodine in the thyroid tissue represents a state in which the thyroxine when produced in an excessive amount is rapidly discharged from the thyroid Thus when patients improve or are relieved of their hyperthyroidism there is an immediate increase in the amount of iodine stored within the thyroid gland The e facts fit most satisfactorily into the theory of hyperiodinism representing hyperthyroidism

Other concepts of thyroid crisis have been offered for consideration Ewald[18] ascribed postoperative crisis to a sudden flooding of the organism with thyroid secretion but he suggested that perhaps it was really due to sudden deprivation of thyroid secretion instead The theory of Letchford[19] stating that crisis was due to thyroid failure appears to have had little basis in fact Pedersen[1] studied the work of Schneider on the serum sodium content and is was not corroborated It was apparent to Pedersen[1] that determinations of the serum sodium have no value in relation to hyperthyroidism Maddock and his associates thought crisis might be ex

plained by ionic disturbance However their experiments led them to conclude that searches for abnormalities in inorganic ion concentrations in blood were unrevealing

All the theories advanced as to the etiology of thyroid crisis have not satisfactorily answered the numerous questions associated with this phenomenal syndrome In the quest for the answer to some of these questions many investigators have been attracted to the role of the liver in thyroid disease

The Hepatothyroid Relationship

The correlation between the largest gland in the human body, the liver, and the potent cervical endocrine gland, the thyroid, was not suspected until 1905 Since then however, pathologists and laboratory investigators have called attention to pathological changes in the liver associated with hyperthyroidism Both experimental and histological evidence wa offered to associate the liver with thyroid dysfunction In spite of all the evidence presented clinicians and surgeons ignored the proffered benefits derived from the laboratory and theorized as to the etiology of thyroid crisis

This stream of experimental pathological studies began in 1905 Schryver observed a greater degree of autolysis in the livers of thyroid fed animals than in the livers of control animals after 24 hours [3] Farrant found that in thyroid fed cats and rabbits in which a modified picture of exophthalmic goiter had been produced exhibited at postmortem examination in addition to other changes fatty degeneration of the liver most marked around the center of the lobules [4] In the same year, Cramer and Krause noted that excessive thyroid administration resulted in glycogen depletion of the liver Kuriyama studied the effect of thyroid feeding on white rats and found that within 3 to 5 days practically all of the animals exhibited a decreased glycogen content of the liver [26] [7] Both Hashimoto [8] and Goodpasture [9] [30] (1921) fed albino rats and rabbits thyroid substance in an endeavor to produce histological changes in the myocardium To their surpri e both produced parenchymatous change in the liver Goodpasture reported a clinical case of hyperthyroidism which exhibited at autopsy progre sive atrophic cirrhosis of the liver with numerous vacuolated nuclei suggesting glycogen depletion Haban (1935) was able by thyroid feeding to produce necrotic changes in the livers of cats and rabbits [31] Moreover he observed a total depletion of glycogen content The e findings were confirmed experimentally by Zeldenrust and Van Beek [3]

Enough additional scattered reports have been recorded in the literature

to establish a definite thyrohepatic relationship Cameron and Karunaratne published an extensive study on this relationship based on 30 cases[33] The coinvestigators attached no special significance to their studies They considered the pathological finding of necrosis as evidence of a severe toxemia based on atrophy and cirrhosis Roessle postulated an hypothesis that in the presence of thyrotoxicosis a toxin is elaborated which acts on the liver because of the detoxifying function of that organ[34] Parturier and Delerue stated that 30 per cent of all patients with hepatic disease present signs and symptoms attributable to the thyroid gland[3] They observed from clinical observation that the effect of the thyroid on the liver is less marked than the effect of the liver on the thyroid, stating "Thyroid function is unlatched only when hepatic function fails"[3] Rome called attention to the frequency with which thyroid failure is complicated by various types of hepatic dysfunction[36] An analysis for toxic thyroid disease was made by Beaver and Pemberton of 107 autopsies at the Mayo Clinic[37] From their survey they believed that in most instances the lesions in the liver appeared to be an integral part of the syndrome of exophthalmic goiter and to be due directly to thyroid intoxication

More specific elucidation of the pathological changes in the liver due to thyroid disease was forthcoming Weller described the usual liver lesion as an interlobular fibrosis with lymphocytic infiltration[38] Among the reports published on the study of liver damage in patients who died of thyroid crisis is that of Youmans and Warfield[39] They reported liver damage in 4 and jaundice in 3 of 5 patients who died in crisis Assmann distinguished a type of hyperthyroidism associated with a rapidly lethal outcome[40] In these cases the more severe conditions passed into acute atrophy of the liver Mahorner reported an interesting case of exophthalmic goiter in which jaundice was a prominent finding[41] The fact that it disappeared less than a month after thyroidectomy suggested to him that liver damage can be caused by thyrotoxicosis and that adequate therapy can restore the liver to normalcy Foss and associates in a study of 11 cases of thyroid deaths found but one normal liver in the cases of true crisis[6]

The above literature describing hepatic disorders in thyrotoxicosis strongly indicates a definite relationship between these two organs, the liver and the thyroid Hence it can be appreciated that both the experimental and pathological evidences previously enumerated indicate a direct relationship between toxic thyroid disease and liver damage Whichever one is accepted as the causative factor is not of primary concern Investigators appear more interested in discovering some method by which the state of the thyroid patient can be estimated in terms of the hepatic factor For this reason attention has been given to formulating laboratory tests on liver function in the thyroid patient

Laboratory Tests on the Liver in Thyroid Disease

Possessing a tremendous reserve capacity, the liver has the ability to function in the presence of extensive parenchymatous damage For this reason an efficacious test of hepatic efficiency must of necessity be most sensitive In the pursuit of the ideal test many procedures have been offered Because the maintenance of a normal blood sugar is a most important function of the liver it is preserved to the very end[4] Of the tests on carbohydrate function the galactose tolerance test has been most favored[4] Judd considered that the methods for detecting hepatic injury by *testing sugar metabolism* were so unreliable as to suggest that they affected only the reserve capacity of that organ[43]

Urea is formed in the liver and uric acid is presumably formed and destroyed in that organ Thus it might be expected that blood urea and uric acid determinations would be a secure calibration of early hepatic dysfunction However such determinations are of little value until liver damage is far advanced[4]

Other studies on hepatic function involved tests for cholesterol The normal values for blood cholesterol are usually 200 mg of cholesterol and 100 mg of cholesterol esters per cent Formerly variations of from 30 to 50 per cent in the ratio were considered normal but now it is believed that the free cholesterol in normal individuals is usually not greater than 30 per cent of the total[4] Changes in the ratio are more important than changes in the concentration of total cholesterol since the esterification of cholesterol esters from cholesterol and high fatty acids is accomplished in the liver *Pickhardt and his associates[44] found the cholesterol of the* blood serum to be a valuable index of hepatic reserve, as did Sperry[4] Other observers however have stressed the ester cholesterol[4]

More specific liver function tests were studied in attempting to evaluate the hepatic status in hyperthyroidism Serum protein values of thyroid patients have been examined by several investigators Bartels found the total serum proteins below normal in 63 per cent of the patients he studied[46] This protein depletion was noted when the patients were first seen or as in 37 per cent of the cases after 10 days of therapy[46] Bartels observed a definite relationship between the level of total serum protein and the severity of the hyperthyroidism This necessitated surgery in stages before the days of the antithyroid drugs Further studies on the inorganic sodium content of blood serum in hyperthyroidism were made by Pedersen[0]

The importance of iodine and its relationship to hyperthyroid states has been previously mentioned With this association in mind most interesting studies have been evolved about the blood iodine test Data have been accumulated which point to the liver as a factor in iodine metabo

lism.[47] Experimental evidence has been offered to indicate that the liver is involved in normal iodine metabolism. Maruno has stated that iodine is excreted with bile.[48] Yuzuriha maintains that the reticuloendothelial system is concerned with the removal of iodine from the blood.[49]

With these studies as a background De Courcy attempted to correlate elevated blood iodine with disturbed liver function.[50] This investigator pointed to the liver as a potent factor in the regulation of blood iodine. He speculated in the absence of proof that the activity of the reticuloendothelial system might play an important part in iodine metabolism. He has tentatively assumed that when the iodine content of the blood is below 100 μg/100 ml, operation can be done with reasonable safety as far as the liver status is concerned.[50]

Of all the tests employed in studying hepatic function in thyroid disease the most satisfactory procedure is the Quick hippuric acid test of the detoxifying function. This method has been employed extensively and successfully at the Lahey Clinic and by Boyce.[4] Boyce used this test in 130 cases of thyroid disease.[51] He concluded that hepatic dysfunction in hyperthyroid disease is more frequent and more serious than was generally realized. He postulated that the progression or regression in function as exhibited by serial Quick tests corresponds to clinical improvement or lack thereof. The degree of hepatic dysfunction is usually related to the clinical severity of the disease and to the degree of toxicity as exhibited by the basal metabolic rate.[51] Improvement in liver function occurs in patients who respond clinically to adequate preparation for operation. This he believes to be a useful test in evaluating the results of therapy. In the employment of the Quick test it is important to know that its greatest value is derived when it is used serially. When it is used in this way it is possible to state that a patient is a good or bad risk from the hepatic standpoint. It is possible to determine from the response to treatment as expressed by this test whether the risk has improved, remained stationary or has become worse.[4]

From all the evidence thus far presented it is evident that many isolated studies have pointed to the importance of liver function in toxic thyroid disease. The various tests employed indicate that hyperthyroidism has a damaging effect on the liver. It is well to mention here that the cephalin flocculation test is not satisfactory for our purposes.

Clinicopathological Evidence for the Hepatothyroid Concept

In the presence of the universal and frequent experimental results clinicians were slow to grasp the full significance of the laboratory evi-

dence in support of the hepatothyroid association The liver and thyroid have a common anatomic relationship in that both are glands Experimental physiopathologists, and later clinicians, have discovered a closer interrelationship between these organs than would appear from this casual anatomic fellowship

It is only within the last decade that the literature has contained clinical references to the hepatothyroid correlation Surgeons now recognize that the liver in thyroid disease is of significant importance Many of them have believed that deaths occurring in hyperthyroidism are chiefly liver deaths Boyce likens thyroid crisis to a "liver shock" type of death, which sometimes follows surgery of the biliary tract [4] Connell believed that the syndrome of rapid hyperpyrexic death occurred only after biliary tract surgery However, he soon abandoned this view and believed it could occur in many other operations

Hyperpyrexic death may follow operations in badly prepared patients It has been allied to thyroid crisis because the clinical picture closely simulates the syndrome seen in untreated or mistreated toxic thyroid disease As to the cause of this calamity of thyroid crisis, Boyce suggests that the toxic overstimulated metabolism results in combustion of the protective glycogen of the liver beyond the degree of safety [4] When this point is reached there develops sudden and extreme hyperpyrexia, an almost uncountable pulse vomiting and diarrhea Restlessness may supervene and may pass into delirium, coma and death

Other authorities have concurred in the thyrohepatic relationship The two Criles, [3] and later Dinsmore [54] [5] have remarked that liver failure is the most common cause of thyroid delirium, mental confusion and death in thyroid crisis

The younger Crile expressed this concept as a problem of hepatic failure and metabolic exhaustion [4] He emphasized the possibility of jaundice Visible jaundice may be present in some cases whereas in others repeated determinations of icteric indices may fail to show any increase above normal level If the icterus index is not elevated there is no way of relating the syndrome to the liver and hence it is called metabolic exhaustion If the presence of jaundice is noted it is classified as hepatic *failure'* [4]

Lahey reported that he was more and more certain that deaths due to hyperthyroidism were chiefly liver deaths [6] He has adduced in support of this thought not only the clinical picture of crisis but the efficacious utilization of intravenous glucose to combat the excessive combustion resulting from hyperthyroid states He believed that with excessive hyperthyroidism goes excessive combustion and when fluid and fuel intake is *inadequate to meet this excessive degree of combustion progressive auto*

combustion occurs with exhaustion of available glycogen and diminution of the glycogen reserve in the liver [1]

Additional studies have substantiated the close relationship between the liver and hyperthyroidism An intimate association between thyroid crisis and functional changes in the liver was suggested by Lord and Andrus on the basis of their study of the plasma prothrombin level in 36 patients with hyperthyroidism [57] Frazier and other surgeons at the University of Pennsylvania published important results on the therapy of thyroid disease as directed to the liver factor [59, 61] Studies by Bartlett confirm and emphasize the importance of liver damage in toxic thyroid disease [6, 63]

Early studies on the pathological picture of the liver in thyroid disease originated in the experimental laboratory With the influence of adrenalin in thyroid disease as a guide Perrazzo in 1934 was able to produce advanced fatty degenerative changes in the liver [64] At that time this finding was considered to be the major pathological lesion observed in many fatal cases of hyperthyroidism Perrazzo accomplished this experiment by the intravenous injection of moderate doses of adrenalin

Shaffer in a study of the livers from 24 fatal cases of toxic thyroid disease found a loss of liver weight fatty infiltration cirrhosis and lymphocytic infiltration in the periportal region often associated with patchy fibrosis [6] Webster and Chesney have shown that when rabbits are fed a diet rich in cabbage a marked degree of goiter results [66] Examination of these thyroid glands showed a considerable degree of hyperplasia which was considered to be compensatory According to Marine a cyanide is the active principle in cabbage [67] Thyroid hyperplasia and even exophthalmos may be produced in young rabbits by the injection of cyanides which greatly lower the oxidation in body tissues Cyanide is toxic to the liver Herein may be the cause for the hepatic picture produced by the investigators analgous to the findings of Shaffer

Boyd has summarized the major pathological hepatic picture in thyroid disease stating There is no constant pattern in the liver lesions but they are essentially congestion and degeneration Fatty degeneration is extremely frequent There may be acute necrosis both focal and central Subacute toxic atrophy may occur with the development of cirrhosis and nodule formation

Anoxia and Hepatic Disease

The increased metabolism of the thyroid patient has been indicted for the facility with which these individuals develop anoxia Several excellent monographs have been written demonstrating the pathological changes wrought in the liver subsequent to anoxia Under such conditions of hepatic

anoxia, the damaged liver appears to accelerate the thyroid gland to hyperactivity In a situation of *this type a mutual distortion of hepatic and* thyroid function results Anoxic damage consumes the hepatic protein elements and the stored glycogen These debilitating factors leave a cadaveric organ which is depleted of all its reserve capacity In this state an additional glycogenolytic *process as demanded by thyroid hypermetabolism* cannot be satisfied This is the basis for liver exhaustion and thyroid death

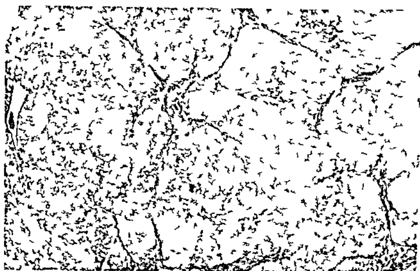


Fig 46 Photomicrograph (25 ×) showing fatty degeneration of the liver giving the picture of fatty portal cirrhosis There is no constant pathologic pattern in the liver lesions of hyperthyroidism but they are essentially congestion and degeneration Fatty degeneration is frequent Other histopathologic changes may be acute liver necrosis both focal and central Subacute toxic atrophy may occur with the development of cirrhosis and nodule formation

Experimental evidence on the extraordinary sensitivity of thyroid fed rats to want of oxygen was recorded by Asher and Duran in 1920[69] They showed that hyperthyroid animals could not tolerate even minor degree of anoxia Two years previously, Streuli and Asher found the converse to be true Thyroidectomized rats were able to tolerate a lack of oxygen which brought normal animals to the point of death by asphyxiation[70]

More recent studies have revealed the effects of anoxia on the liver in hyperthyroidism Hepatic distress subsequent to want of oxygen is logical Liver cells are closer to asphyxiation *than other cells because only 25* per cent of their blood supply is supposedly arterial[71] Reinwein and Singer led one to assume that increased oxygen demand by the liver in a hyper

thyroid state leaves a narrow vital margin of safety, which is easily destroyed[7] In the same trend of thought McIver has shown that the liver is particularly susceptible to injury under conditions of hyperthyroidism[73]

More recent experiments by McIver and Winter elucidate the effect of anoxia on the liver during artificial hyperthyroidism in rats[4] These investigators studied the behavior reaction of hyperthyroid and normal animals when exposed to low oxygen atmosphere (11 per cent) The normal animals showed no signs of acute distress except for a slight increase in respiratory rate The hyperthyroid animals were restless and apathetic They studied 26 rats 17 of which had received injections of crystalline thyroxine Nine of the 17 hyperthyroid rats died after varying periods of anoxia The first 2 hours in the low oxygen atmosphere seemed to be the most critical for the hyperthyroid rats

The effects produced by lack of oxygen were similar to those of glycogen imbalance The studies of McIver confirmed some aspects of the work produced by Lewis and his associates[75] In their studies on the role of the adrenal cortex in acute anoxia they confirmed the previous conclusions of Evans[6 7] All showed that hepatic glycogen tends to fluctuate in rats exposed to low atmospheric pressure

Knowing *de facto* that deleterious damage occurs in the liver due to the factors presented pathological studies have confirmed definite anatomic alterations in the liver Scholars concerned themselves with this problem as early as 1913 Farrant produced histological changes in the liver by administering thyroxin[8] Similar results were produced by Gerler who employed large and even fatal doses of thyroxin[9] McIver attempted in his experiments to use nonlethal doses The amount employed was merely sufficient to produce a hyperthyroid state In this way he hoped to avoid the pathological changes in the liver caused by overdosage His plan was to produce alterations in hepatic tissue by anoxia in the hyperthyroid animals His subjects were all healthy and free from disease This healthy state was important because Haban in studying the effects of crystalline thyroxin injections on the liver found tissue change only when some intercurrent infection was present[80]

The most lucid study on the histological pathology of the liver was made by McIver in his experiments[5] He has shown that the pathological material from the rats killed after receiving crystalline thyroxin in nonlethal doses failed to reveal any notable histological abnormalities of the liver However when the cells were compared with those of normal well fed rats the cells in the livers of thyroxin treated rats were more homogeneous and compact The appearance of the cells however did not differ essentially from the hepatic cell of a starved animal McIver attributed this analogy to the fact that hepatic glycogen was diminished markedly

Anoxic changes have been recorded in hyperthyroid rats As might be expected, the lesions in animals that died or were killed after short exposures to oxygen deficit were not advanced Those changes consisted of fatty changes, vacuolization of the cells and engorgement of the blood vessels In the animals exposed for longer periods the degenerative changes were severe and widespread A summation of the pathological findings may be stated as

1 Necrosis most pronounced around central veins
2 Marked engorgement of the sinusoids especially in the vicinity of the central veins
3 The cell outlines were often lost
4 The cells in the areas of degeneration showed an affinity for eosin
5 Pyknotic nuclei were found to be associated with the loss of cell boundaries

From the pathological data already presented the noxious effect of anoxia upon the liver is obvious It is further evident that in the patient with hyperthyroidism every precaution is essential in order to avoid the complications associated with a low oxygen tension This problem gives rise to the choice of anesthesia for a toxic thyroid patient who is a potential candidate for anoxic anoxia For this reason Colcock has stressed the point of anesthesia Nitrous oxide was abandoned because too little oxygen (usually only 10 per cent) was available to the thyroid patient whose oxygen demand was 2 to 3 times that of the average patient [81] Avertin enjoyed popularity and was frequently employed with nitrous oxide Avertin a respiratory depressant has in the experience of Cole and Brunner, occasionally increased the toxicity in patients with severe hyperthyroidism [8] These problems on anesthesia brought to light the rationale and use of oxygen in the postoperative treatment of hyperthyroidism as well as the value of oxygen during thyroidectomy [83 84]

Comments and Conclusions on Thyroid Crisis

*From a literary review it can be stated that many surgeons and investi*gators have studied the role of the liver in thyroid disease Of all these, several have intimated and few have definitely incriminated the liver as the ent of distress in thyroid crisis This review of the subject leads one to believe that the liver is in some way, the organ to be indicted as a potent factor in the pathogenesis of thyroid crisis

Among the reasons for this belief are

1 The clinical picture of crisis closely simulates exhaustion resulting from hepatic hyperpyrexia

2. Experimental evidence and the morbid anatomical findings indicate the close association between hyperthyroidism and the liver.
3. Boyce's results with the Quick hippuric acid test of liver function have been offered as proof of liver damage occurring as the result of thyroid disease.
4. The physiological imbalance and pathological changes in the liver due to anoxemia have been established. Anoxia in hyperthyroidism is common knowledge.
5. The interrelationship between hyperadrenalism, hepatic glycogenolysis and the experimental production of toxic thyroid signs by injections of adrenalin have been emphasized.

The premise of this discussion, therefore, is that the most important organ, exclusive of the thyroid itself, concerned in the production of thyroid crisis is the liver. Physiological failure of this organ will result in so-called thyroid death. This conclusion is reached following clinical observation, experimental data, laboratory function tests and objective findings as revealed by pathological anatomy.

The causative or exciting agents in the production of hepatic imbalance may be multiple or a combination of several. Of all the phases discussed on this aspect of the subject, the most plausible possibilities are hyperadrenalism and hepatic anoxia. These states, either alone or acting synergistically in the presence of hyperthyroidism, may be the fundamental destructive influence in the causation of crisis. Hyperadrenalism may be the activator in depleting the liver of its available glycogen. In this state of insufficiency, the hepatic anoxia resulting from increased hypermetabolism produces the lethal blow which precipitates crisis and the eventual hyperpyrexic thyroid death.

Attention is called especially to anoxia. It is strongly believed that the acute pathological lesions found in the livers of patients dying from hyperthyroidism are the result of anoxia. This is a problem of clinical importance since the occurrence of anoxia in hyperthyroidism is commonly known. Especially is this of great concern in the production of postoperative crisis when tracheal obstruction, pulmonary edema or other complications may interfere with adequate pulmonary aeration.

One is not unmindful of the fact that the liver may be merely a solitary reflection of a generalized somatic picture. Anoxemia may affect all the organs in the body in the production of crisis. The liver, however, has been stressed in hyperthyroidism because its normal physiology and pathological physiology can be tested with ease and because this organ is subjected to routine examination at autopsy. That physiological discord in crisis is revealed in other organs and tissues of the body is appreciated. Even though this is known, it is believed that the fulminating picture of

crisis and death occurs only when the liver has been burdened beyond its ability to compensate for the demands required under the stress and strain of thyrotoxicosis

On the basis of all the proof offered as to the role of the liver in hyperthyroidism, a notation on preoperative preparation is not amiss Fortification of the liver should be of primary concern This should include a liberal carbohydrate diet glucose by mouth or by vein, (preferably supplemented by decholin), a definite proportion of protein in the diet, vitamins and blood transfusions In this regard Lahey has stated 'There is one point regarding the treatment of thyroid crisis and that is the need to give these patients fluid and glucose constantly and not intermittently There is a tendency to be intermittent This is unwise since it leaves periods during which the excessively activated metabolism will still consume the liver reserve It is necessary in patients with thyroid crisis to give them fluids and glucose quite constantly throughout the entire day if one wishes to extricate them from these serious thyroid states "[17]

The topic of preoperative preparation brings to mind the diversity of opinion as to multiple state operations in thyrotoxic patients Decades ago those patients with toxic goiter known to be recalcitrant to iodine therapy and considered unfavorable operative risks were subjected to multiple stage operations It is felt that the beneficial effects of this procedure were not due to the simplicity of the operation Credit must be given to the fact that the respite between stages gave the patient a preoperative regimen on more than one occasion This preparation directed toward 'building up the patient inadvertently fortified the liver against a future thyroid crisis In keeping with this thought it is believed that multiple stage procedures were not the answer to the prevention of crisis but rather that rehabilitation of the liver was the *sine qua non* of prophylaxis

One of the purposes of this discussion is to bring to the attention of the surgeon that prophylaxis against thyroid crisis is preferable to therapy after the syndrome has developed Fortunately crisis is rarely encountered today With this idea before the reader, the writer has accentuated the value of preoperative rehabilitation of a liver suspected of dysfunction and of fortifying an apparently normal liver In the preoperative care of a patient suspected of being a candidate for thyroid crisis the following is a recommended regimen

1 Complete bedrest
2 Lugolization
3 Sedation (phenobarbital, bromides)
4 Propylthiouracil is administered until B M R is near normal Lugol's iodine or organidin is given simultaneously

5 Oxygen tent to combat anoxia and hyperthermia if necessary By placing a patient in a tent an evaluation of the psyche can be estimated If the patient is perturbed by the tent he is not psychologically prepared for operation
6 Glucose intravenously plus amino acids and vitamins (for three days)
7 Blood transfusion to combat anemia
8 Cardiac therapy when indicated
9 The patient's psyche is strongly considered and treated

The hyperthyroid individual is treated as a psychosomatic entity The best guides to the patient's response to therapy and calibration as to operability are

1 The patient's mental attitude
2 The fall and maintenance of a normal or near normal pulse rate
3 A consistent fall and maintenance of a lowered basal metabolic rate

It is believed that in stressing the role of the liver in crisis future clinical and laboratory investigators may find the solution to this intricate problem

In conclusion it may be reiterated that clinical observation has suggested a possible hepatic basis for the pathogenesis of thyroid crisis The physiologist and experimental clinician have presented evidence substantiating this belief Both gross and microscopic hepatic studies have augmented the proffered evidence The liver therefore when distressed due to glycogen depletion may be accused as the death producing factor in accelerated hyperthyroidism By promulgating this concept it is hoped that interest will be stimulated toward that organ From this stimulus some future investigator may confirm or deny the master role of the liver as the major etiological agent in the production of thyroid crisis

Addenda

A R Hunter of London has reported the beneficial effects of chlorpromazine as an aid in cooling the patient in thyroid crisis Following thyroidectomy one of his patients went into thyroid crisis Her temperature rose to 105 F (40 6 C) and the pulse rate was 200 Twenty four hours after surgery it was apparent that a thyroid crisis was developing The patient was packed in ice and was in addition given a test dose of chlorpromazine 25 mg orally followed by 50 mg 4 hours later A further 50 mg dose was given every 8 hours during the subsequent 72 hours Her temperature fell steadily Subsequently her condition improved steadily but the administration of chlorpromazine was continued The patient re

covered During the administration of the drug the patient had ice bags placed under each axilla, over the abdomen, and both groins The patient was placed in an oxygen tent The author stated that he believed that the essential problem in thyroid crisis was to reduce the excessive metabolic rate He believed that in the past there had been no completely effective method of doing this and for this reason the mortality in crisis had been very high In the case he reported the combination of cooling, with the prevention of shivering by the administration of chlorpromazine, seemed to answer the problem[613]

Hyperthyroidism and Myasthenia Gravis

*On infrequent occasions myasthenia is an associated symptom of hyper*thyroidism Bartels of the Lahey Clinic stated that the incidence of combined hyperthyroidism and myasthenia gravis is less than 1 in 3 000 hyperthyroid patients[8]

Thorn and Eder have summarized the various types of muscular dysfunction which may complicate hyperthyroidism as follows[11]

1 Exophthalmic opthalmoplegia
2 a Acute thyrotoxic myopathy
   b Thyrotoxic periodic paralysis
   c Chronic thyrotoxic myopathy
3 Myasthenia gravis with hyperthyroidism

The purely thyrotoxic myopathies always improve as the patient is restored to an euthyroid state Since the control of myasthenia gravis invariably requires additional therapeutic measures, its recognition as a *complication of hyperthyroidism is important The reported cases suggest* that the control of the hyperthyroidism may have a variable effect upon the coexistent myasthenia gravis in some cases relieving and in others intensifying the muscular weakness

The cause of myasthenia gravis is unknown but the defect appears to be at the myoneural junction with a failure of passage of impulses from the nerve to muscle probably resulting from a deficiency of acetylcholine Daily administration of maintenance doses of neostigmine or prostigmin bromide orally is usually successful in alleviating the muscular weakness Since thymectomy introduced by Blalock in 1939 has been successful in relieving symptoms in certain cases of myasthenia gravis partial extirpation of this organ may be performed[8]

The manifestations of thyrotoxic myopathy and myasthenia gravis are quite similar but they can be differentiated While both may give rise to external ophthalmoplegia ptosis is rarely seen in hyperthyroidism Likewise, dysphagia and dysphonia do not occur in hyperthyroidism but are

frequently present in myasthenia gravis The greatest aid to the diagnosis of myasthenia gravis lies in the response to the intramuscular injection of neostigmine

Improvement in the symptoms of myasthenia gravis with the onset of

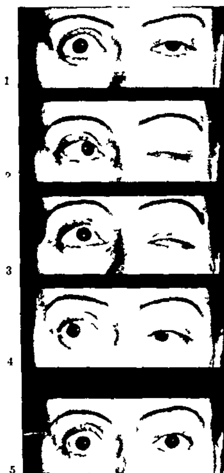


FIG 47 Patient with myasthenia gravis (1) Ptosis the most common symptom of myasthenia is frequently associated with limitation of extraocular movements (2 3 4) In this patient left ptosis is accentuated on left lateral gaze (2) The left lower lid elevates slightly on right lateral gaze (4) Characteristically visual acuity accommodation and pupillary responses are unimpaired Retraction of upper right lid seen here is an uncommon development Effects of neostigmine are shown in picture 5 An injection of neostigmine was given and in 15 or 20 minutes the patient got up out of bed walked around raised her arms and was almost normal (Walsh F B Myasthenia gravis and its ocular signs Tr Am Ophth Soc 41 556 1943)





FIG 48 (*top*) Photomicrograph demonstrating multiple lymphoid germinal centers in the thymus gland of a patient with myasthenia gravis The lower photomicrograph is that of a normal thymus gland presented for comparative study Approximately 6 × [145]

hyperthyroidism may occur in some patients Relief of the patient's symptoms may result if both a thyroidectomy and a partial thymectomy are performed

The course of myasthenia gravis is often characterized by remissions

but recurrences and progre ion ultimately occur in the majority of cases Although prolonged spontaneous remis ion is the exception this must be con idered in evaluating any form of therapy for mya thenia gravis

It i intere ting to note that Merten of Germany has cured everal ca es of myasthenia gravis by surgical denervation of the carotid sinus He has preceded his operative denervation with a therapeutic test con si ting of novocaine nerve block of the area [604]



Fig 48 (*top*) Photomicrograph demonstrating multiple lymphoid germinal centers in the thymus gland of a patient with myasthenia gravis The lower photomicrograph is that of a normal thymus gland presented for comparative study Approximately 6 × [illegible]

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The course of myasthenia gravis is often characterized by remissions

The isotope in organic iodine contains a large dose of radiation which is readily delivered to the overactive thyroid cells. If the dose is sufficient, actual necrosis of the thyroid cell can result.

The normal thyroid gland picks up about 20 per cent of an ingested dose of radioiodine while the gland of the patient with hyperthyroidism will collect about 80 per cent. In myxedema little or none is collected by the gland. Both beta and gamma rays are emitted by radioactive iodine. The beta rays have a maximum range of only a few millimeters and radiation can thus be confined almost exclusively to the tissue holding the radioactive isotope. Collection of radioiodine by the thyroid usually occurs within a few hours. What is not absorbed is excreted readily by the kidneys.

The principal isotopes used are I^{130} (with a half life of 12 hours) and I^{131} (with a half life of 8 days). Fifty per cent of the total radiation dose from I^{130} is delivered in the first 12 hours and 90 per cent within 36 hours. Determination of the amount required by a patient is partly guesswork since an estimation of the weight of the gland must be made in calculating dosage. Generally 5 mc to 25 mc will be effective. The calculated dosages in which internal radiation has been successful are from 500 to 2500 roentgens which agree with figures for external radiation generally used. Certain prerequisites for successful treatment have been advised. For example, the patient should have received no previous iodine for at least one month; he should be available for close follow up and he should be given routine iodinization with Lugol's a few days after his original dose of radioiodine. Not all radiologists agree that Lugol's is necessary in every case. Contraindications to radioiodine include large goiters which require surgery to relieve pressure symptoms, pregnancy and kidney disease.

Effects of Radioactive Iodine

Within a few days after an ingested oral dose of I^{130} the gland becomes firmer and slightly tender. The beginning of relief of symptoms is variable, being from a few weeks to a few months. Some proponents of internal radiation claim that an 80 per cent cure rate is possible. In view of the fact that a very large number of patients treated with the isotope have not been reported in the literature, this figure must be accepted cautiously. Among 22 patients, 14 made a good response to one dose of radioiodine and the remainder required a second or third dose. Two of the group remained mildly hyperthyroid and 4 developed myxedema. Reactions resembling roentgen ray sickness occurred in 6.

Much remains to be learned about the ultimate effects of radioactive iodine. What it does to glomeruli and tubules in the presence of renal disease is unknown. Also unanswered is the question of whether it will pre

11

Management of Hyperthyroidism

According to the major pathology noted in the thyroid gland, hyperthyroidism falls into three categories. These are

1. Primary hyperthyroidism with or without exophthalmos
2. Adenomatous goiter with secondary hyperthyroidism (this includes toxic adenoma)
3. Thyroid cancer

In recent years several new discoveries have been made which when applied to thyroid disease have proved beneficial. Certain physiologic interpretations have added to the understanding of the ability of the gland to concentrate the iodide ion (often spoken of as iodine trapping). This trapping is not the same as the thyroid's physiochemical ability to elaborate iodine into thyroid hormone. This knowledge has been unfolded by observation of the pharmacologic reactions following the administration of goitrogenic drugs.

Thiocyanate prevents the concentration of iodide within the thyroid gland and the thiouracil compounds allow the absorption of iodide but inhibit the physiochemical transformation of iodine into the hormone. It is further believed that the antithyroid drugs actually prevent the formation of thyroxin.

With this newly gained physiochemical and pharmacologic knowledge a great change has taken place in the treatment of hyperthyroidism. Present day treatment of hyperthyroidism resolves around a choice of three methods. Two are medical and one is surgical. The medical methods are radioactive iodine and the thiourea drugs; the surgical method is thyroidectomy.

Radioactive Iodine

The introduction of radioactive iodine therapy (1941) and the utilization of the thiouracil drugs (1943) have provided the medical therapeutic agents. The radioactive isotopes of iodine give off an intense radiation. The mode of action in suppressing hyperthyroidism can be explained physiologically. The thyroid cell needs iodine for hormone production and the hyperthyroid cell more than the normal cell is "hungry" for iodine. Hence, these hyperthyroid cells readily grasp the iodine containing the radioactive isotope

The isotope in organic iodine contains a large dose of radiation which is readily delivered to the overactive thyroid cells. If the dose is sufficient actual necrosis of the thyroid cell can result.

The normal thyroid gland picks up about 20 per cent of an ingested dose of radioiodine while the gland of the patient with hyperthyroidism will collect about 80 per cent. In myxedema little or none is collected by the gland. Both beta and gamma rays are emitted by radioactive iodine. The beta rays have a maximum range of only a few millimeters and radiation can thus be confined almost exclusively to the tissue holding the radioactive isotope. Collection of radioiodine by the thyroid usually occurs within a few hours. What is not absorbed is excreted readily by the kidney.

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Much remains to be learned about the ultimate effects of radioactive iodine. What it does to glomeruli and tubules in the presence of renal disease is unknown. Also unanswered is the question of whether it will pre-

dispose to neoplasia and whether or not radiations will damage surroundin tissues Many years will pass before these questions can be answered no

ISOTOPE LABORATORY

Ambulatory
Wh l hair
Str t h

I otope Laboratory Number
Date

Name Admission Number
Address
Age Sex Occupation Div
Clinical Diagnosis

Brief Resume of History

Examination or Treatment Desired

Radioa t ve Iodine 131 Tracer Study Therapy

H s pati t b d.

1 Iodi i any form l l st 4 week	Y s	N	
2 Thyr id i any form in la t week	Yes	No	
3 Thiocyan i wi hin l t 2 week	Y s	No	
4 A ti thyroid or If drug within last 2 weeks	Y s	No	
5 La g d f br mid withi la t 2 weeks	Y s	No	
6 Gall bladd r o kid y studi with dy withi l t 4 week	Y s	No	
7 B o hog aphy withi l st 2 month	Y s	N	
8 My l g phy at any time	Y s	No	
9 C rtiso e r ACTH	Yes	N	
10 Previ Iodi ptak tudy	Y	N	Fi dings
11 B sal M t boli t	Y s	N	Fi di gs
12 B ood Ch l t l e s	Y	N	F di g

Radioactive Phosphorus 32 Tra er Study Therapy

Most re I Wbc Diff B E My J St Seg L M
Dat Rbc Hb Plat l ts
Oth r I otope Tracer Study Therapy

M D

FIG 49 Copy of a standard chart from I otope Laboratory This chart is completed before the patient receives any isotope

only because prolonged observation is imperative but also because the general use of these radioactive agents will remain limited for a time in certain areas

Radioactive iodine is admini tered either in a single do e or in divided

ISOTOPE REPORT

HOSPITAL ______________________

P t t ______________________ D t ______________________

Act ty ______________________ Amou t ______________________

Att nd ng physic an ______________________ Ck u ______________________

THYROID UPTAKE

	TIME	SIG	NET K	TOT	%	C.S.S
Background						

P tie t

Ant			
R S d			
L. Sid			
P t			
T t l			

A g						(1)
R sid t						(2)
St nd d						(3)

3 − 2 = Cor ct St nd d ______ (4)

$p\ t\ \ker\left[\frac{(\ )}{(\ )}\right] \times 100 =$ ______ %

Oth A

____
ISOTOPE LABORATORY

Fig 50 This chart is filled out after the patient has received a radioactive substance

doses according to the radiologist's preference for technique Relief from thyrotoxicosis is complete if a sufficient dose of radioactive iodine is given Surprisingly, no great damage to the parathyroid glands has been reported following the administration of radioactive iodine

The major disadvantage of radioactive iodine is the possibility of delayed carcinoma formation It should be given, therefore, only to patients in whom this question may not arise It may be given to other individuals in whom this disadvantage is outweighed by greater disadvantages which would result if another form of therapy was chosen It is the therapy of choice in the geriatric patient who is a poor operative risk or in an individual who has had recurrence following one or two thyroidectomies

Radioactive iodine is not the treatment of choice in adenomatous goiter with hyperthyroidism for the following reasons

1 There is a high incidence of carcinoma in adenomatous goiter
2 Dosages would have to be high and would have to be repeated at intervals
3 The size of the goiter may not recede If it does nodules may persist which necessitate surgical removal

Madigan and King of Australia report the study of a research group This group including physician radiotherapists physicists a pathologist and a biochemist undertook to investigate the following [0]

1 The value of physical indices concerning uptake and excretion of tracer doses of radioactive iodine (I^{131}) as an indication of thyroid function
2 The value of protein bound iodine as an index of thyroid function,
3 Comparison of the value of physical indices protein bound iodine and basal metabolic rate estimations in the same group of patients compared to clinical assessment
4 Comparison of various physical indices to determine the most useful
5 Clinical trial of I^{131} as a therapeutic agent in hyperthyroidism and carcinoma of the thyroid
6 Investigation of superior mediastinal tumors with tracer doses of I^{131} to detect thyroid tissue if present
7 Establishment of a method of radioautography

The extensive paper and two others to be published later report the results of the joint project carried out at the Royal Melbourne Hospital The first part of this paper is concerned with the clinical assessment of the 140 tracer tests carried out on 114 patients 72 of these tests were made on 66 subjects with normal thyroid function 65 on 45 patients with thyrotoxic hyperthyroid function, and 3 tests on 3 patients with hypothyroid

function (myxedema) Clinical assessment gave correct classification for 128 of 140 tracer tests Physical indices gave correct classification for 113 of the total 140 performed Protein bound iodine estimation gave correct classification for 111 tests of a total 131 performed The basal metabolic rate gave correct classification for 40 tests and inconclusive or incorrect results for 36 of the total of 76 performed The analysis of 23 patients with hyperthyroidism who were treated with I^{131} revealed that 3 have since died of cardiac failure existent at the time of I^{131} therapy and of hypertensive or rheumatic causes in addition to a thyrotoxic element Two of these patients had their thyrotoxicosis controlled by a single dose of I^{131} and the other died two months after a single dose with only partial control Twenty patients are still alive Ten of these had their hyperthyroidism controlled and have been under observation for 6 months to 3 years Of the remaining 10 patients 4 improved but were only partly controlled The period of observation since the last dose has been between 2 and 6 months Five patients have been in a nontoxic state since their last therapy dose was given 3 to 5 months ago insufficient time has elapsed to determine whether their condition will be controlled Because a superior mediastinal tumor may be a retrosternal thyroid mass 10 patients with mediastinal masses were studied by tracer tests with radioactive iodine Notwithstanding certain difficulties such as the close proximity of the superior mediastinum to the thyroid there was sufficient uptake in the mediastinal mass in 6 of the 10 patients tested to indicate the thyroid tissue content This conclusion was later verified at operation in each of these 6 patients The therapeutic use of radioactive iodine in malignant lesions of the thyroid was limited Only 5 of 17 patients with suspected thyroid carcinoma were given therapeutic doses of radioactive iodine the others being regarded as not suitable for this treatment [3, 7]

At this stage of the discussion I should like to record the story of a patient who was among the first individuals to receive this therapeutic form of iodine

Case History of a Patient Treated with Radioactive Iodine In March 1947 Mrs M S a 41 year old housewife was first seen by the author as a hospitalized patient At that time she was transferred from the gynecological service to surgery because of symptoms indicative of hyperthyroidism She was admitted to the hospital primarily for an elective vaginoplasty Her hyperthyroid history was of 3 years duration

The classic symptomatology was present including an enlarged thyroid gland and exophthalmos At the time of admission she weighed 158 lbs and her B M R was +64 Subsequently it was +37 +35 and +15 No antithyroid drug was employed Electrocardiogram demonstrated tachycardia consistent with hyperthyroidism no organic cardiac disturbance was recorded Preoperative x ray studies failed to reveal any evidence of metastases

A significant fact in the past history was a left-sided kidney operation performed in 1939 Intravenous pyelograms taken in 1947 demonstrated that a partial left nephrec

tomy had been performed The remaining left renal tissue and the right kidney were normal (Urinalysis was negative) The reason for the partial left nephrectomy could not be determined

On March 25 1947 a total thyroidectomy was performed At the time of operation malignancy was suspected in the gross specimen The histological report was adenocarcinoma

Postoperatively the patient was given radiation therapy to the neck A total of 41 6 R was given following radiation she was given radioactive iodine I[131] (8 day half life) The radioactive iodine was obtained from the Clinton Laboratories Oak Ridge Tenn



Fig 51 This photograph was taken several months after the administration of radioactive iodine There is noted a marked gain in weight myxedema and a persistence of exophthalmia (more prominent on the left side)

Twenty four cc was administered orally Each cubic centimeter contained 3 1649 mc of the isotope A total of 76 mc was given to the patient This was a total of 10 108 mc/hrs (76 × 133) Following this procedure the Geiger counter demonstrated a generalized disturbance

On June 6 1947 her B M R rose to +77 blood cholesterol was 160 mg

A tracer dose of 5 mc of radioactive iodine was given X rays of the skeletal system did not reveal any metastases The patient was readmitted to the hospital from August 25 1947 to September 2 1947 for complete studies No evidence of metastases was found

The patient left the hospital refused further treatment and would not allow any doctor to visit her Finally a photographer was sent to her home The result is produced herewith

At the time the photograph was taken she had gained weight and evidence of myxedema was present.

The patient was not seen again until September 2? 1919 at which time she was treated in the clinic. Her weight was 199½ pounds. She had marked myxedema for which thyroid extract was prescribed. On October 29 1919 her weight was 208½ pounds. A notation was made that she was five months pregnant. Her weight increased by November 17 to 210½ pounds and by December 9 to 213 pounds. At this time she was taking 5 grains of thyroid extract. X ray studies failed to demonstrate any recurrence of the thyroid lesion.

She was not seen again. A follow up letter was sent to her home. Her daughter replied that the patient died on January 26 1950 following the birth of a normal son.

A letter was sent to the hospital where the patient expired. No autopsy was performed. Death was attributed to renal failure secondary to toxemia of pregnancy.

Summary. This patient with carcinoma of the thyroid gland was treated by surgical removal of the gland, radiation therapy and radioactive iodine. Following this therapeutic regimen she developed myxedema which necessitated the administration of thyroid extract. The patient became pregnant and died following the birth of a normal infant. Death was attributed to toxemia of pregnancy. No autopsy was obtained. In the absence of definite anatomical findings revealed at autopsy no positive conclusions can be reached. However, it is known that radioactive iodine is excreted by the kidney. This patient's previous kidney operation plus the clinical evidence of renal failure with a toxemia of pregnancy strongly suggests that kidney damage was present at the time of death.

This report, although incomplete because of the failure to obtain an autopsy, nevertheless is of value as one of the first medical histories of a patient who was among the early recipients of radioactive iodine.

Treatment of Thyrotoxicosis with Potassium Perchlorate

An interesting report has been published in the English literature on the use of potassium perchlorate in hyperthyroidism. Potassium perchlorate inhibits the uptake of radioactive iodine by the thyroid of animals as well as of man. It has been used in the treatment of patients with thyrotoxicosis. Morgans and Trotter used potassium perchlorate in the hope that it might prove effective in controlling thyrotoxicosis without exposing the patient to the risk of the toxic side effects sometimes seen with the thiouracil drugs.[181] Perchlorate acts only on the iodide concentrating mechanism of the thyroid. Thiouracil, on the other hand, leaves this mechanism unaffected but prevents the oxidation of iodide and its subsequent incorporation into protein molecules to form thyroglobulin. Thiouracil is therefore effective whatever the concentration of iodide in the blood, but perchlorate would become ineffective with blood iodide levels

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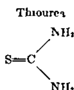
Treatment of Thyrotoxicosis with Potassium Perchlorate

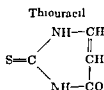
An interesting report has been published in the English literature on the use of potassium perchlorate in hyperthyroidism. Potassium perchlorate inhibits the uptake of radioactive iodine by the thyroid of animals as well as of man. It has been used in the treatment of patients with thyrotoxicosis. Morgans and Trotter tried potassium perchlorate in the hope that it might prove effective in controlling thyrotoxicosis without exposing the patient to the risk of the toxic side effects sometimes seen with the thiouracil drugs.[161] Perchlorate acts only on the iodide concentrating mechanism of the thyroid. Thiouracil, on the other hand, leaves this mechanism unaffected but prevents the oxidation of iodide and its subsequent incorporation into protein molecules to form thyroglobulin. Thiouracil is therefore effective whatever the concentration of iodide in the blood, but perchlorate would become ineffective with blood iodide level

sufficiently high to raise the concentration within the thyroid to the level normally attained by the gland's iodide concentrating mechanism. A patient in whom thyrotoxicosis is controlled by perchlorate would be liable to relapse if his blood iodide level were suddenly raised, for example by the administration of an iodide containing cough medicine. This is a theoretical difficulty, but so far Morgans and Trotter have not observed it. It might also be expected that if a thyrotoxic patient is prepared for operation with perchlorate, similar difficulties would arise when iodide is added during the final stages to reduce the vascularity of the goiter. Potassium perchlorate was made up in either 50 or 200 mg tablets. These were *administered either once or twice daily*. The patients were usually seen at monthly intervals. In a dosage of 400 mg daily, potassium perchlorate was effective in controlling thyrotoxicosis in most patients. The rate of response appeared to be somewhat slower than with methyl thiouracil, and in one of 25 previously untreated patients control was not complete. When patients receiving maintenance doses of methylthiouracil were given potassium perchlorate instead, control of the thyrotoxicosis was maintained in all but 2 of 64. The average dosage necessary was 2 to 4 times that of methylthiouracil. No toxic effects were seen in 108 patients treated with potassium perchlorate except signs of gastric irritation in 2 patients with a history of dyspepsia.[161]

The Antithyroid Drugs

Within our own lifetime, we have seen the remarkable results achieved in the treatment of thyrotoxicosis by means of thiourea, thiouracil, itrumil and other similar sulfur compounds. These drugs have a more pronounced and striking effect in abating the toxic symptoms than any other medication known to mankind. Their mode of action provides a new and fascinating study in the field of the physiological chemistry of the endocrine system.





Astwood's introduction of the thiouracil compounds showed that these drugs block the elaboration of iodine into the hormone.[06 707 71] With this blockage there is an increase in the activity of the pituitary on the thyroid cells causing hyperplasia. The anatomic result of these drugs on

the thyroid gland is the direct opposite of the effect produced by iodine Iodine when given with the thiouracil compounds, is able to produce involution of the gland in spite of the thiouracil It is possible to control the thyroid function of almost any degree of toxicity by varying the dosage of the antithyroid drugs It is a common practice to administer large doses initially and then to reduce the dosage when a normal metabolic rate has been reached

The judicious use of the thiouracil drugs results in a satisfactory control of hyperthyroidism Usually, there is a very high recurrence of toxic symptoms following the withdrawal of these drugs Therefore the drug must be administered until the metabolism is normal for 6 to 16 months in order to assure a cure Even after this long period of treatment 50 per cent have a recurrence Thus another form of therapy may be necessary to produce a cure even after prolonged use of the antithyroid drug

In the beginning thiourea and thiouracil were the only drugs available Thiourea was bitter to the taste so that thiouracil was preferred by the patient This drug however was quite toxic and constant observation was imperative Other new drugs which had less toxic reactions were developed These were methylthiouracil itrumil mercaptoimidazole tapazole and propylthiouracil The latter drug is preferred because of its low toxicity More recently two iodinated thiouracil compounds have been manufactured Use of these iodinated drugs has not been extensive so that an exact evaluation of them cannot be made at this time

The possibility that thiourea compounds might have a carcinogenic tendency is a warning against their use in certain individuals For this reason it is not the treatment of choice in simple thyroid adenoma where the incidence of a hidden malignancy may be as high as 8 per cent It should not be administered over a long period of time in adenomatous goiters for the same reason In any patient who has received the antithyroid drugs over a period of years the possibility of malignant changes should be remembered Any unusual increase in size of a goiter under this form of therapy especially if this increase is asymmetrical should be an indication for surgical intervention

Attention must be called to the fact that the antithyroid drugs may result in some disturbance to sensory nerves These toxic effects are loss of smell and taste following the prolonged use of propylthiouracil and methylthiouracil These neurotoxic manifestations should be remembered when the thiourea drugs are employed In the cases reported to date these sensory disturbances were not permanent The discontinuation of the drug and high doses of vitamin B complex usually ameliorates these sensory toxic symptoms

Effects of the Antibiotics on the Thyroid Gland

At any symposium on the thyroid gland, the question almost always raised is "What are the negative or positive effects of the antibiotics on the thyroid gland? Recently Calesnick, Harris and Jones in an issue of *Science* (**119** 128 1954) reported that penicillin as well as aureomycin produced a goitrogenic and antithyroid effect in experimental animals They base their conclusion upon the increase in the weight of the thyroid gland and the decreased uptake of I^{131} in these animals Inasmuch as the antibiotics are so widely used in the treatment of human diseases it is well to have a definite answer as to whether penicillin and/or aureomycin can alter the activity of the thyroid gland Experimental work of recent origin strongly indicates that penicillin and aureomycin are not goitrogenic and do not decrease the uptake of I^{131} in experimental animals or by inference in human beings As a general statement therefore it may be stated that there is a lack of sufficient evidence to warrant the belief that there is any direct action by the antibiotics on the thyroid gland [343 3 9]

The Antithyroid Action of Para Aminosalicylic Acid

It has been known for years that many aminophenol compound have a goitrogenic action Astwood showed in 1943 that p aminobenzoic acid inhibited thyroid gland function in rats The closely related substance *p aminosalicylic acid and its sodium salt have been extensively used in* the treatment of tuberculosis in England Macgregor and Somner [3] cite observations by others that make it apparent that p aminosalicylic acid can in some circumstances when used in normal dosage for the treatment of tuberculosis in man produce clinical hypothyroidism They tried to assess the true incidence of goiter and hypothyroidism in a fairly large group of patients being treated with this drug The thyroid function of the patient was evaluated with radioactive iodine They found an incidence of goiter with hypothyroidi m developing in 23 per cent of the patients under observation Studies with the isotope revealed that all patients receiving p aminosalicylic acid showed changes in thyroid function Although the goitrous and hypothyroid state induced by *this drug is usually* reversible on the withdrawal of the drug the authors feel that thyroxine should be given to all patients in whom a goiter is noted or to whom p aminosalicylic acid is given for more than six months

Surgical Treatment

Mortality and morbidity following thyroid procedures are rapidly fading away These results are due in great measure to the excellent preoperative

regimens employing the antithyroid drugs Today, the thyroid patient is operated upon just like any normal person undergoing surgery No stealing of the thyroid under avertin anesthesia is now necessary Among the advantages of surgical intervention are the following

1 The pathology is definitely established
2 The presence of cancer is detected and radical surgery can be performed immediately
3 Prolonged medical therapy is eliminated
4 The goiter is removed by surgery Antithyroid drugs may even increase the size of the gland Radioactive iodine may diminish the size of the goiter but the hidden possibility of malignancy at some future date remain
5 Operative therapy produces no carcinogenic activity

Moreover, thyroidectomy, for many years has been a widely and highly effective method in the control of exophthalmic goiter After proper preparation it can be carried out with a minimal surgical mortality except in the unusual and very complicated case Thyroidectomy is followed by postoperative myxedema in less than 5 per cent and by recurrent or persistent hyperthyroidism in a little more than 5 per cent of patients subjected to surgery The incidence of parathyroid insufficiency or injury to the recurrent laryngeal nerve resulting in permanent paralysis of the vocal cords is very low in the hands of the competent thyroid surgeon In the majority of patients treated surgically the basal metabolic rate decreases to normal or to near normal levels within three weeks after operation Therefore surgery must be considered as a rapid and highly effective method of controlling hyperthyroidism

Practical Aspects of Thyroidectomy

Certain aspects of thyroidectomy which have proved beneficial are presented here in summary

Exposure The usual collar like incision of the skin is made about 2 to 4 cm above the sternoclavicular junction A low incision is made in order to facilitate exposure of the lower thyroid areas, wherein vital structures are found In addition the low incision eliminates dead space where fluid may accumulate since the area close to the clavicle is more fixed It must be remembered that thyroid incisions are made while the patient s head is extended Following operation with the head in a normal position the incision may descend as much as 2 to 3 cm The skin flap is dissected up to the thyroid cartilage in order to allow exposure of the thyroid poles

Division of Prethyroid Muscles Whether to divide the prethyroid muscles or not is a matter for the individual surgeon to decide Any method

to which the surgeon has become accustomed is the best in his hand The author s per onal preference is to divide the muscles high at the junction of the upper and middle thirds in order to avoid the ansa hypoglo si nerve and the superior laryngeal nerve This high division does not interfere with the healing of the low skin incision, nor does the division of these muscles increase serum collections The excellent ex posure of the thyroid gland, when the muscles are divided far outweighs any objection offered against this procedure

So called Thyroid Capsule At the operating table, the surgeon does not find a true thyroid capsule which will enable him to enucleate the gland It is true, however, that there are certain lines of cleavage which form a sheath with attachments to the thyroid gland The so called capsule is a reflexion of a plane of the deep cervical fascia A layer of thin areolar tissue is found on the inner surface of the sternothyroid muscle This layer is associated with the pretracheal fascia which in turn continues as the anterior portion of the sheath of the thyroid gland This anatomic for mation permits the identification of cleavage planes, which when followed mobilize the thyroid gland and gives rise to the faulty interpretation that a separate thyroid capsule completely encircles the gland If one will re call the fascial planes of the neck, it will be evident that no true thyroid capsule exists

These fascial planes may be grouped as follows

First plane Subcutaneous fascia and platysma mu cle

Second plane Fascia of sternocleidomastoid and trapezius muscles

Third plane Fascia of the sternohyoid mu cle (N B The second and third fascial planes blend po teriorly)

Fourth plane Fascia of the sternothyroid muscle and the fascia of the carotid sheath This fascial plane blends with the pretracheal fascia and the layer of fascia (so called capsule) encompas ing the thyroid gland

Fifth plane This is a po terior layer called the prevertebral or retro visceral fascia

The fifth plane does not concern the thyroid surgeon but is important to the thoracic surgeon who must deal with ingested foreign bodies

Thyroid Vessels An axiom of major significance to the thyroid surgeon is never to clamp blindly in a pool of blood There are so many vital structures in a small circumscribed area that the clamp may crush what is not intended to be clamped For this rea on it is preferable to ligate the major thyroid vessels first then any technique which pleases the operator may be followed according to his individual plan The major vessels in question are the superior and inferior thyroid vessels the

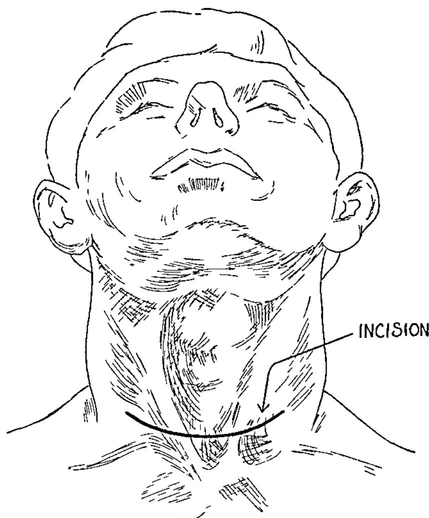


FIG 52 This drawing illustrates the usual collar like incision which is performed as an initial step in a classic thyroidectomy It is noted that the chin is extended maximally the thorax is forward and the neck assumes a goiter position This anatomic position is obtained by placing the patient on the operating table in a concave position with the head markedly elevated and the feet raised to a comparable height with the thorax In this position the surgeon then incises the skin placing the incision a little higher than the location he desires it to be ultimately (because the incision will descend from 2.5 cm to 4 cm after healing depending upon the size of the original underlying goiter) One should remember that a thyroid incision is made with the eye and not with a measuring rule

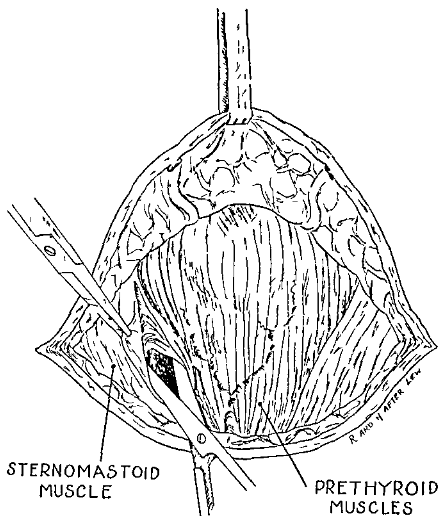


Fig 53 An exemplification of the height to which the skin flap is dissected This dissection is carried superiorly to the thyroid cartilage On occasion the skin flap will include the platysma muscle when it is visible In patients with a well developed neck the skin flap is raised to above the thyroid notch (inferior border of the thyroid cartilage) Elevation of the skin flap is necessary in order to adequately expose the thyroid gland especially the superior thyroid vessels at the upper pole of the gland This diagram depicts the separation of the sternocleidomastoid muscle from the prethyroid muscles The incision liberates the sternocleidomastoid muscle enabling the assistant to retract it laterally for a more satisfactory division of the prethyroid muscles on that side (Thyroid cartilage is represented by shaded area in midline below thyroid double hook)

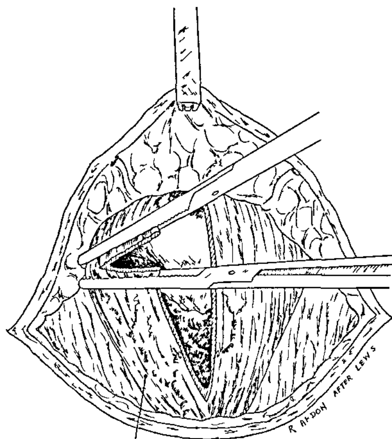


FIG 54 A wider exposure is possible with retraction of the sternocleidomastoid muscle Clamps are then placed across the prethyroid muscles at the junction of the middle and upper thirds of these muscles Division of the muscles at this level protects the nerves going to the prethyroid muscles and an excellent exposure of the gland results In addition a division of the muscles at this location can be repaired with a resulting suture line that is high under the skin flap without interfering with the closure of the skin and at the same time eliminating the possibility of adherence of the skin to the underlying muscle

middle thyroid vein and the ima vessels There is no middle thyroid artery Double ligation of the arteries results in a diminution of blood supply to the gland so that it may be dissected with a less bloody field The middle thyroid vein should be ligated and divided as soon as it is

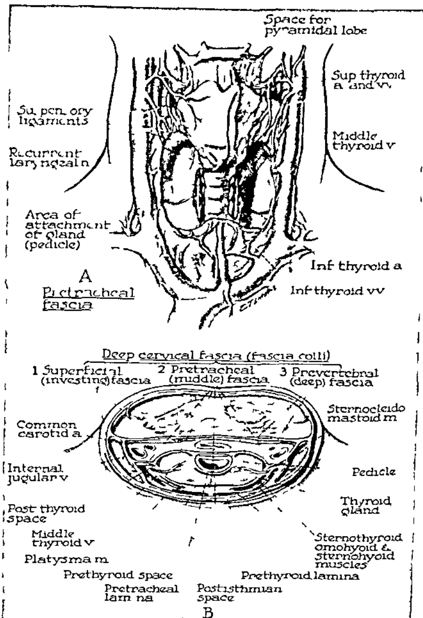


Fig 55 A surgical anatomic exposure of the neck to illustrate the fascial layers of the neck[**]

A The suspensory ligaments of the thyroid gland are shown passing from the inner margins of the gland to the cartilaginous framework The blood vessels and the recurrent laryngeal nerve as related to the pretracheal fascia are demonstrated

B The deep cervical fascia (fascia colli) is pictured in cross section This fascia is conceived as consisting of three layers superficial or investing layer middle or pretracheal layer and the deep or prevertebral layer The anterior and posterior thyroid spaces (also termed the pre and post thyroid spaces) are seen in relation to the middle thyroid vein

identified because when damaged, it bleeds briskly like an artery The same is true of the thyroid ima vessels

The superior thyroid artery is the first branch of the external carotid artery The superior thyroid vessels are located between the pretracheal and prethyroid laminae and are found a little above the thyroid cartilage The inferior thyroid artery is larger and carries more blood than the superior vessel It arises via the thyrocervical trunk from the subclavian artery, emerges from behind the carotid sheath penetrates the posterior aspect of the pretracheal fascia and passes medially to the gland where it may divide into two or more branches The inferior thyroid veins and ima vessels are situated inferiorly between the prethyroid and pretracheal fascial laminae Knowledge of their location makes possible their rapid identification and immediate ligation

The Laryngeal Nerves Possible injury to the laryngeal nerves is always thought of by the thyroid surgeon Both laryngeal nerves superior and inferior supply the sensory and the motor innervation of the larynx

The superior laryngeal nerve arises from the vagus (see Figs 62 to 65) Both motor and sensory this nerve divides into two branches one external and one internal The external branch (motor) supplies the cricothyroid muscle and serves as the tensor of the vocal cords The internal branch (sensory) innervates the mucosa of the larynx epiglottis and part of the pharynx Section of the superior laryngeal nerves causes a loss of sensation in the laryngeal mucosa and paralysis or relaxation of the cricothyroid muscles resulting in a lowering of pitch and a diminution in the clearness of the voice The loss of sensation causes an inability to perceive the entrance of foreign bodies into the larynx The superior laryngeal nerve can be protected if the superior pole is ligated as the gland is retracted downward and if the pole is ligated even with the point of entrance of the blood vessels into the pole

The inferior laryngeal (recurrent laryngeal) arises at the level of the subclavian artery on the right side goes around the artery and ascends toward the thyroid gland The left recurrent arises from the vagus in front of the aortic arch and ascends toward the left lobe of the thyroid Both right and left recurrent nerves may course outside or inside the inferior thyroid artery or between its branches

The inferior laryngeal nerve supplies the motor branches to the intrinsic muscles of the larynx It enters the larynx behind the inferior cornu of the thyroid cartilage It is known that the inferior laryngeal nerve is composed of two bundles of fibers one for the adductor and the other for the abductor muscles Injury to one inferior laryngeal nerve affects the adductors but respiration continues The loss of the voice may be temporary

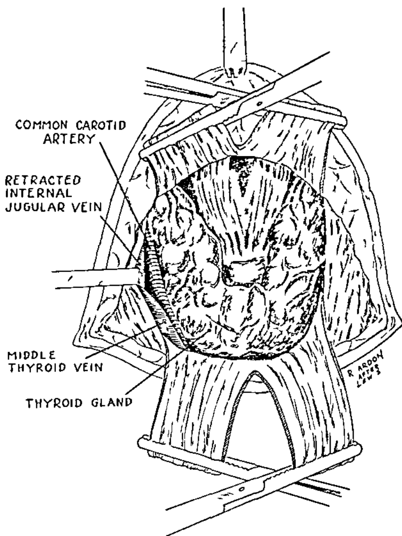


Fig 56 The next step in performing an orderly thyroidectomy is to ligate and then divide the middle thyroid vein This is done easily if the assistant retracts the internal jugular vein laterally by means of a blunt retractor After the middle thyroid vein is divided the underlying common carotid artery is brought into view The assistant then replaces his retractor so that the common carotid artery is now pulled gently in a lateral direction This facilitates exposure of the superior thyroid artery which is doubly ligated in continuity and then divided The superior pole of the thyroid gland is thus liberated By gentle retraction inferiorly the bare area of the trachea is exposed on the posteromedial aspect of the thyroid lobe This is a bloodless area and permits a prompt liberation of the upper third of the thyroid lobe

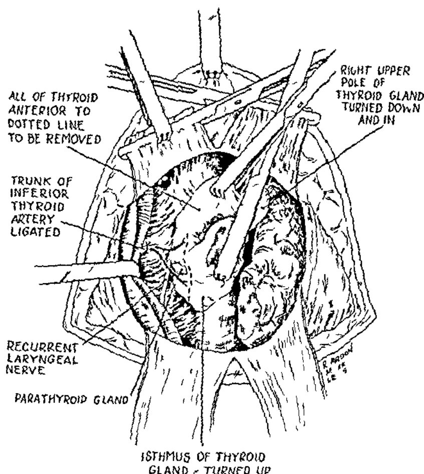


Fig 57 This diagram depicts the right thyroid lobe retracted inferiorly and medially after the superior pole has been ligated and divided The bare area of the trachea lies immediately beneath the upper thyroid double hook clamp The retraction of the lobe in this position allows a clear identification of the inferior thyroid artery which is shown ligated in this drawing The dotted line along the lateral surface of the thyroid lobe indicates the site where the incision will be made into the gland tissue all the parenchyma above this line will be removed in toto The close proximity of the parathyroid gland to the inferior thyroid artery is demonstrated

since the unimpaired vocal cord may pass over the middle line and contact the paralyzed one Phonation then occurs

Unilateral injury to the abductor fibers results in a fixed midline paralysis of the vocal cord Respiration continues as well as phonation be

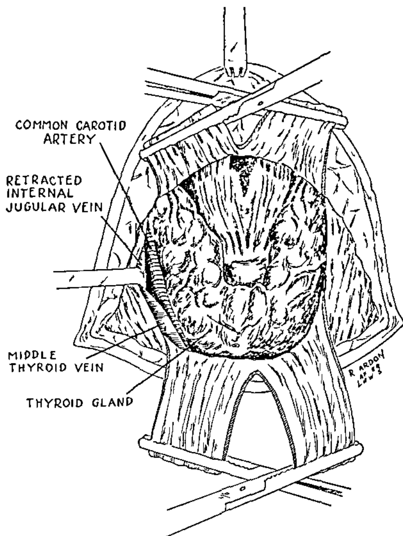


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cau e the impaired cord allows ample breathing space and brings both cords into close approximation

If both nerves are injured bilateral abductor paralysis results The vocal cords are in permanent adduction The patient can speak but can not breathe Tracheotomy then must be performed

In order to avoid injury to the recurrent nerves some surgeons have advocated a routine identification of the nerve In such cases the inferior thyroid artery is the guide to finding the nerve Routine nerve identification is not always necessary especially for the noninitiated in this procedure Other precautions mu t be taken however

Most injuries to the recurrent nerves occur at the lower pole of the thyroid gland and at the point of its entrance to the larynx through the inferior constrictor pharyngeal mu cle The surgeon therefore must avoid undue trauma in these areas and he should expo e the posterolateral surface of the lobe by retracting it forward Thereafter constant visualization of the operative site with a knowledge of the anatomic pathway (unless *the nerve travels within the gland as an anomaly*) will prevent nerve injury

A preoperative laryngoscopy will *identify the existence of any paralysis*

B Another approach of the inferior thyroid artery in which the vessel forms an upward arch and then descends behind *the thyroid lobe to enter the gland* This arch may be so high in some patients as to reach the level of the superior thyroid artery

C When the inferior thyroid artery pas es from below upward in an acute angle as shown *here it is most difficult to* demonstrate at the operating table The surgeon may be lulled into a false sense of security in not being able to demonstrate the artery and he may believe that it is absent It is rarely absent and can be demonstrated by lifting the lower pole of the lobe out of its resting position As an aid in visualization and identification a blunt retractor is placed on the common carotid artery and it is retracted laterally The retractor should be placed lower than the point of exit of the artery

D This illustration exemplifies a common anatomic finding in which the artery bifurcates before *entering the gland at a distance* quite away from the margin of the lobe so that it may be erroneously thought that there are two arteries

E Another illu tration of a preglandular bifurcation in which the artery divides behind *the common* carotid artery This type of vessel is very deceiving in that one branch only may be ligated and the other missed completely The result is that bleeding becom s brisk when the gland is incised It is well to remember (when bleeding is severe and difficult to control) that a second branch of the inferior thyroid artery may be the cause Location of this vessel and its proper ligation will result in a less bloody operative site

F Rarely does one encounter the ab ence of an inferior thyroid artery It does occasionally occur however and in its place one can find a thyroidea ima artery This artery enters the lobe in the lower *pole in a location* corre ponding to the point of entrance of the superior thyroid artery so that if an imaginary line is drawn from one to the other there would be an almost immediate and accurate connection between them

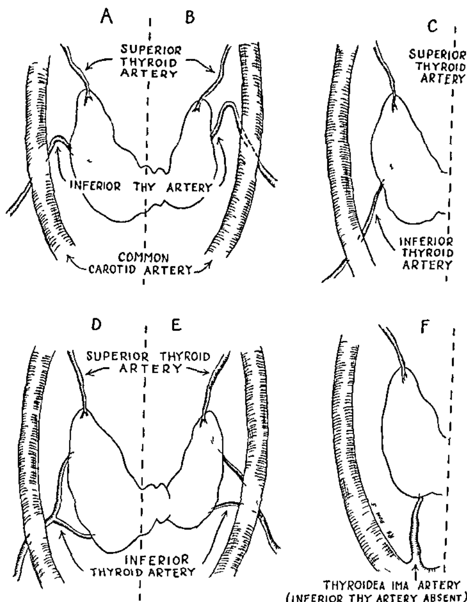


FIG 58 These drawings exemplify the various positions assumed by the vascular structures of the thyroid gland The important arterial structures are the superior and inferior thyroid arteries and the major venous structures are the superior middle and inferior thyroid veins plus the thyroidea ima vein

A The superior thyroid artery is almost always consistent in its entrance to the thyroid lobe at its superior pole The inferior thyroid artery varies much more than the superior one This diagram shows the most common pathway of the inferior thyroid artery as it enters the gland directly

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of the nerve due to a displacing pressure resulting from retrosternal or adenomatous projections of the thyroid gland When there is a preoperative

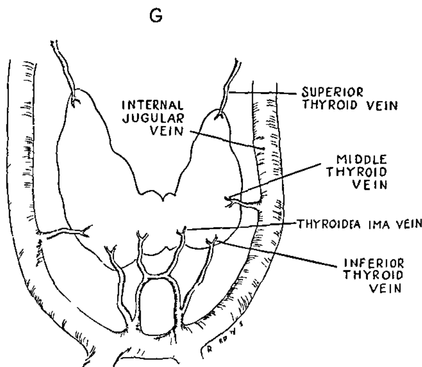


Fig 58 *G* A diagrammatic representation of the venous return of the thyroid gland Generally speaking the veins in the superior poles correspond to the arteries on either side The middle thyroid veins are usually found alone and the inferior thyroid vein is more consistent in location than the inferior thyroid artery The vein is usually found leaving the inferior pole of the lobe on either side More medial than the inferior thyroid vein is the thyroidea ima vein which is easily torn if the gland is retracted quickly In order to accurately liberate the thyroid gland from its bed and perform a neat dissection one must ligate and divide these venous channel When ligation is performed the ligatures should not be placed too close to the internal jugular vein because the ligature can slip easily when the assistant attempts to sponge the operative field A simple sliding motion along the course of the internal jugular vein is often sufficient to disrupt what seems to be a securely tied ligature

paralysis of the recurrent laryngeal nerve the surgeon knows in advance that the operative procedure can not produce *this* damage However, it is to be remembered that the danger of nerve injury is increased greatly when a second operation is performed on a small adherent toxic thyroid gland Thought must also be given to the fact that a partial paralysis or paresis

in the decibel measurement of the voice may last for 6 to 8 weeks Under this circumstance there is no need for tracheotomy since the patient has no respiratory distress It is therefore not in any way similar to injuring the superior laryngeal nerves bilaterally

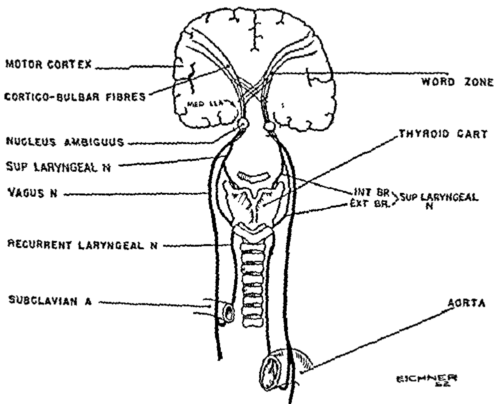


FIG 61 Concept of the origin and course of the recurrent laryngeal nerve (Ross D E Paralysis of recurrent laryngeal nerve Am J Surg June 1953)

Simon s law postulates the consecutive triad of changes in nerve injury

1 Adduction loss occurs leaving the vocal cord in the adducted position
2 Tension loss relaxes the cord further
3 Adduction loss in the final stage shows the vocal cord in the partially abducted midcadaveric position

Injury to the recurrent laryngeal nerve may result in the following alteration in vocal cord function

1 Respiration is obstructed causing stridor
2 Phonation is affected resulting in speech defects

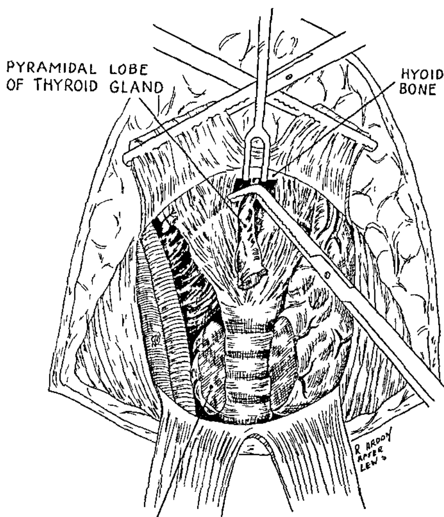


Fig 60 A pyramidal lobe may be present in about 40 to 50 per cent of patients with hyperthyroidism It should be removed especially in patients with exophthalmic goiter because otherwise it may be the cause for a persistence of hyperthyroid symptoms Moreover it may enlarge following thyroidectomy resulting in a visible mass in the center of the neck This diagram shows that the pyramidal lobe often extends high up in the neck often as far as the hyoid bone The proper placing of a retractor at the point where the prethyroid muscles separate will enable the surgeon to remove the pyradimal lobe in toto This illustration shows the ligation of the superior thyroid vessels These vessels should be checked before closing the neck because these ligatures may slip easily when the patient commences to react from the anesthesia Slight coughing or the exertion concomitant with nausea and/or vomiting may be sufficient to produce a hemorrhage The thyroid remnants are seen before they are sutured to the trachea

3 Expulsion of foreign bodies is affected producing an interference in the cough mechanism

Avoiding Removal of Parathyroids Accidental removal of the parathyroid glands results in tetany The safest method of preserving these structures is not to include them in the portion of thyroid being resected These structures are usually found in the posterolateral surfaces of the thyroid gland

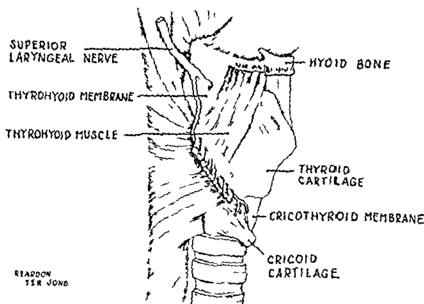


Fig 64 Lateral view illustrating the position and course of the superior laryngeal nerve and its relationship to the outer prethyroid muscles and the thyrohyoid muscle When the sternohyoid and the sternothyroid muscles are divided the underlying nerve may be injured

The parathyroid gland is kidney bean in shape mahogany brown in color and has molded edges it is concave on the inside and convex on the outside The parathyroids change color becoming darker upon exposure to the air because of embarrassed circulation

Before discarding any thyroid tissue from the operating table the surgeon should examine all specimens to ascertain the presence of any accidentally removed parathyroid These glands are commonly found along the main vascular channels

If a parathyroid has been removed unintentionally it should be transplanted It is necessary to return the gland to surroundings similar in tem

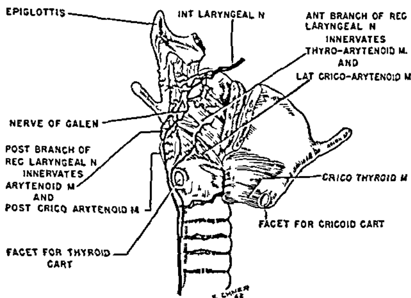


Fig 62 Lateral view of the recurrent laryngeal nerve Note the nerve passing behind the cricothyroid articulation (Ross D F Paralysis of recurrent laryngeal nerve Am J Surg June 1953)

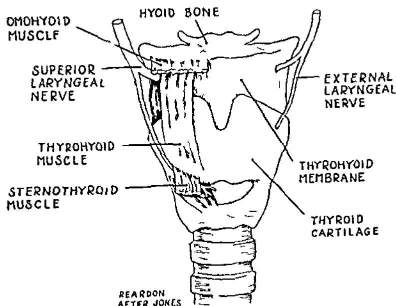


Fig 63 This drawing illustrates the position and course of the superior laryngeal nerve in an anterior view The close proximity of the nerve to the thyrohyoid muscle is evident Dissection of the thyroid gland in this locality presents the danger of possible nerve injury if one fails to recall the location of the nerve

Closure of Operative Site Prior to closing the wound the anesthetist is requested to flex the patient's head This procedure relaxes the muscles under tension and also may stimulate bleeding from any vessel insecurely ligated Thus any bleeding point can be seen and controlled before the incision is closed

The prethyroid muscles are approximated with interrupted mattress sutures (black silk) and accurately closed in the midline If the muscles

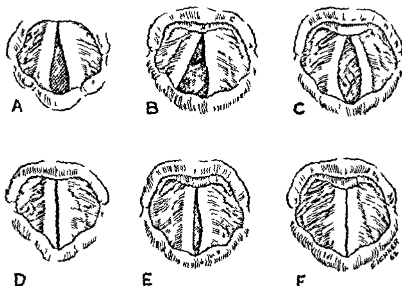


Fig 66 Anatomic position normal and abnormal of the vocal cords *A* Normal larynx in inspiration *B* Unilateral paralysis in median position *C* Bilateral midline paralysis (cadaveric position) *D* Normal larynx in phonation *E* Unilateral paralysis in phonation *F* Bilateral midline paralysis (assumed in some cases) (Ross D E Paralysis of recurrent laryngeal nerve Am J Surg June 1953)

are not approximated satisfactorily the skin flap may become adherent to the trachea If this does occur the skin moves with every act of swallowing resulting in an unsightly deformity

Finally closure of the wound is accomplished without drainage If deep bleeding has been controlled with difficulty and the surgeon anticipates the possibility of bleeding a drain should be inserted deeply into the operative site and allowed to emerge from the lateral edge of the operative skin incision

Minor bleeding from the skin edges is usually no problem Bleeding of this type can be controlled by metal skin clips Metal clips do not alter the

perature and physiochemistry to those from which it came For this reason it is best to transplant a parathyroid into the thyroid remnant It is not definitely known how many glands must be removed before tetany occurs However the removal of one gland usually does not result in tetany with three active glands remaining

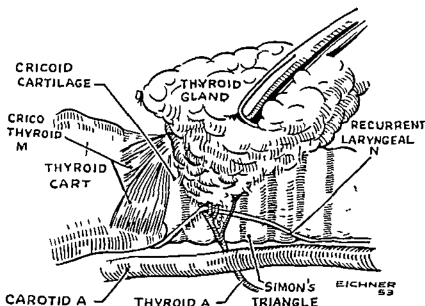


Fig 65 This drawing illustrates how the recurrent laryngeal nerve is angulated forward in Simon s triangle by traction on the thyroid lobe Nerve injury does not usually occur in this triangle when there is no traction although this area is a valuable asset in identifying the nerve However when traction occurs the nerve is angulated and injury may occur at the angulation point when a clamp is placed in this region As the drawing indicates the point of nerve injury is higher than Simon s triangle (the level of the first tracheal cartilage) (Courtesy of Donald E Ross of Los Angeles)

The Thyroid Remnant Following thyroidectomy bilateral stumps of the lobes remain Their cut surfaces are rough with minute bleeding not often visualized In order to eliminate the rough surfaces and to control the bleeding, the remnant may be sutured against the sides of the trachea thus eliminating the possibility of having the rough cut surface of the remnants becoming adherent to the sternothyroid muscle Absorbable catgut is best for this type of suturing but fine black silk may be employed as well Tracheal sutures must be placed with care in order to prevent tracheal perforation or an excessive reaction resulting in a tracheitis

healing of the skin flap if they *are not pressed too tightly In persons* with a keloid tendency (ascertained by the presence of keloid formation in other operative scars) it is preferable to employ silk to close the skin

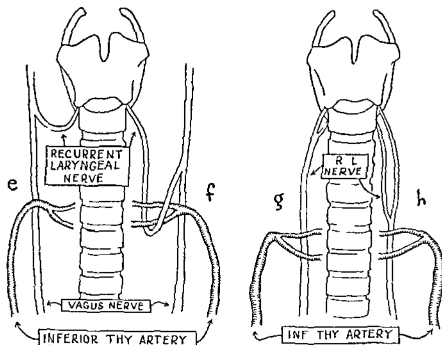


FIG 67 *E* Another situation in which the recurrent laryngeal nerve does not descend into the mediastinum It makes an acute angle almost straight from the vagus nerve to enter the larynx at a level beneath the inferior constrictor muscle

F In this drawing the nerve actually encompasses the inferior thyroid artery descending in front of it and then going upward behind the artery In this situation injury to the nerve *is almost inevitable unless a dissection of the artery is carried out* with much diligence

G A dichotomous recurrent laryngeal nerve is here demonstrated This is described as an extralaryngeal division of the nerve There is seen a division of the nerve just before it enters the larynx

H Another illustration of the same division of the nerve However in this drawing the extralaryngeal division is lower than in *G* and is closer to the inferior thyroid artery

If the surgeon finds keloid formations on the body of his thyroid patient radium may be used prophylactically This form of therapy may be started 8 to 10 days following thyroidectomy If radium does not prevent keloid formation it may reduce the severity of it Beveling of the skin incision and a careless inexact approximation of the skin flap after surgery may be factors in accentuating keloid formation

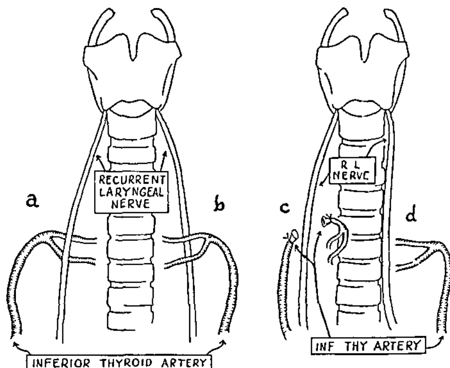


Fig 67 This series of drawings illustrates the various sites of the recurrent laryngeal nerves and the devious pathways that it may follow in relationship to the inferior thyroid artery A knowledge of the location of this nerve will help avoid injury to it Therefore if it is at all possible the nerve may be identified and then the surgeon can proceed without fear of damaging it

A A portrayal of the recurrent laryngeal nerve passing anterior to the artery When the nerve is present in this area it is more easily demonstrated and at the same time is less easily injured than when located elsewhere (i e when the nerve passes posterior to the artery) In this location the nerve is lifted with the gland when it is retracted anteriorly and medially out of its bed Attempts at identification and ligation of the inferior thyroid artery therefore may inadvertently result in clamping cutting or ligating the recurrent laryngeal nerve

B This is the most frequently seen location of the recurrent nerve as it rests behind the inferior thyroid artery Dissection and demonstration of the inferior thyroid artery and its ligation will reveal the underlying nerve

C This diagram demonstrates the division of the inferior thyroid artery As a fundamental principle it is well to remember that the nerve is almost always found in relationship to the artery Therefore in a difficult situation identification and division of the artery may often facilitate the demonstration of the recurrent nerve as it emerges from the mediastinum and proceeds upward into the larynx

D This drawing shows the position the recurrent nerve may take in patients with large cervical substernal and intrathoracic goiters As the goiter increases in size it gradually compresses the recurrent laryngeal nerve against the trachea Clinically this may produce voice changes At the operating table the nerve may be so close to the trachea that it is adherent to it This makes identification and demonstration of the nerve most difficult and often impossible

healing of the skin flap if they are not pressed too tightly In persons with a keloid tendency (ascertained by the presence of keloid formation in other operative scars) it is preferable to employ silk to close the skin

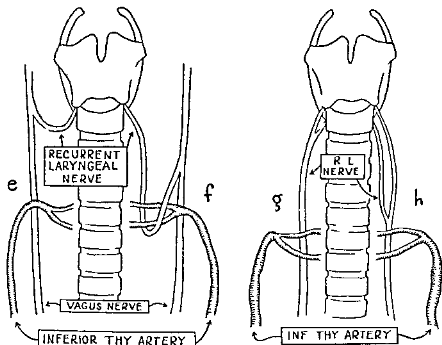


FIG 6 *E Another situation in which the recurrent laryngeal nerve does not descend* into the mediastinum It makes an acute angle almost straight from the vagus nerve to enter the larynx at a level beneath the inferior constrictor muscle

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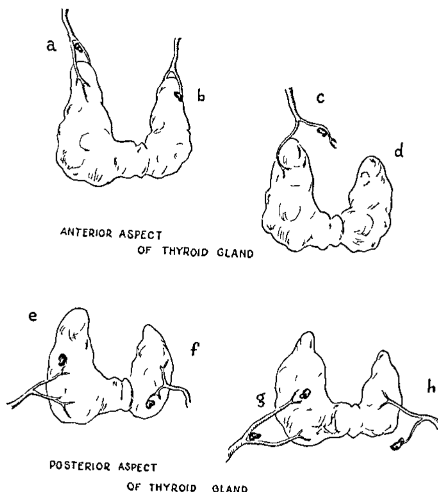
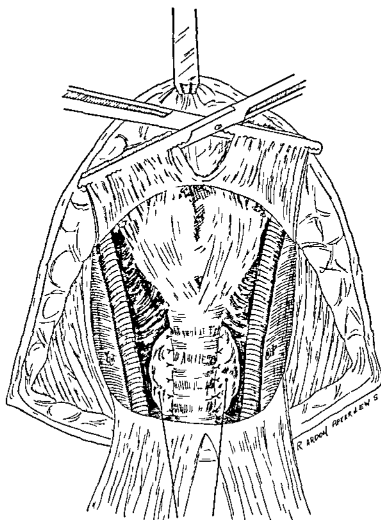


FIG 68 These drawings show the positions of the parathyroid glands on the anterior and the posterior aspects of the thyroid gland In general the parathyroid gland is in the vicinity of an artery In figure D the incompleted dotted area represents a parathyroid gland close to the larynx In this location the gland can be removed with the thyroid tissue and go undetected Figure H depicts a parathyroid gland as an appendage to the terminal branch of an inferior thyroid artery It is well to remember figures A to H when one explores the neck for a parathyroid adenoma In such cases it is an aid to realize that the tumor is close to an artery Secondly that if the adenoma cannot be found then the inferior thyroid artery should be traced throughout its entire course All the branches should be followed with care given to those branches going in the direction of the mediastinum A parathyroid adenoma is frequently found in the superior mediastinum Thirdly figures E to H illustrate the location of the parathyroid glands on the posterior aspect of the thyroid gland These areas may be the sites for an adenoma For this reason a complete exploration of the neck for a parathyroid adenoma may necessitate a division of the thyroid isthmus and a lateral release of the right and left lobes in order to prove or disprove the presence of the tumor at this location



REMNANTS OF THYROID GLAND
SUTURED TO TRACHEA

Fig 69 *When both lobes of the thyroid have been removed and also the pyramidal* lobe (when it is present) the remnants are sutured to the trachea These remnants are approximated close to the trachea with fine 00 catgut of fine black silk (our preference is to use black silk throughout) Suturing of these remaining thyroid areas to the trachea controls any bleeding from the gland and will prevent secondary delayed hemorrhage Note the ligated sites of the middle thyroid veins bilaterally

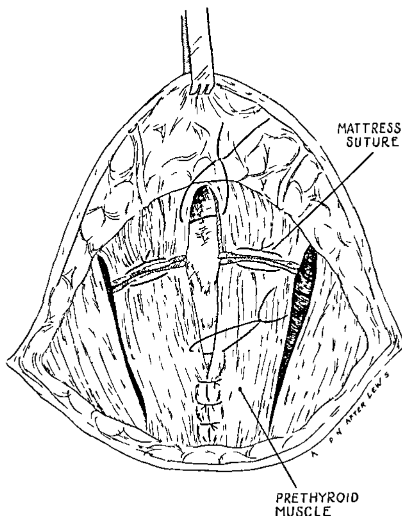


Fig 70 When no bleeding is in evidence and the head has been flexed then the muscles are reconstructed The prethyroid muscles are approximated with mattress sutures of silk The muscles are sutured in the midline with interrupted single black silk sutures A satisfactory closure of the muscles is one in which there is no irregular surface which may become adherent to the skin and no visible trachea which could adhere to the skin flap When the skin is closed with metal clips the sutured muscle is high above the line of clips

Treatment of Post-Thyroidectomy Tetany

Tetany following thyroidectomy may be latent or manifest When it manifests itself, it usually occurs on the second postoperative day It may occur sooner if the blood calcium levels fall rapidly The clinical revelation of tetany demands that some measures be instituted to counter

act this di tre ing complication In the tre atment of tetany c alcium salts parathyroid hormone and dihydrot achy terol have been used A product of v alue is Hyt akerol which is prepared in oil and in c ap ules for oral ad mini tration When given orally the do e i 6 to 20 cap ules daily (or 3 to 10 cc parenterally) according to the severity of the tetany The drug is given until the tetany is relieved On occa ion a weekly maintenance do e is *needed (2 to 14 cap ules or 1 to 7 cc) depending upon the blood* and urine calcium level which should be determined at st ated intervals During the cour e of Hytakerol therapy c alcium lactate or gluconate (from 10 to 15 Gm) hould be given daily Patients with tetany are ad

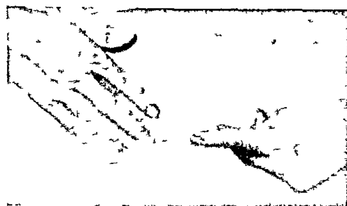


Fig 41 The characteristic attitude of the hand in tetany The fingers of the left hand are flexed at the metacarpophalangeal joints and extende l at the interphalangeal joints The thumb is adducted across the palm of the hand Right hand is normal and is shown for comparison (Graham F A Surgical Diagno is Philadelphia W B Saunders Co 19 0)

vised to drink milk in large quantitie Tetany following thyroidectomy i usually transient in type and of short duration

It has been demonstrated experimentally that the blood supply to the parathyroid gland is not di turbed even after the ligation of all four thyroid arterie [09] The abundant collateral circulation established be tween the internal laryngeal internal mammary and the transtracheal vessels together with the preservation of the po terior facial layers over the tracheal allows for an adequate blood upply to the parathyroid glands For this reason the surgeon does not fear ligating the major vessels going to the thyroid gland because he is aware of the fact that he cannot injure the parathyroid glands in this way One should see however that the para thyroids are not removed accidentally in the operative specimen

It is possible that a patient may develop chronic hypoparathyroid tetany following thyroidectomy

Case report A case of this type in a 54 year old woman has been reported by Blackburn in the Medical Journal of Australia (1 928–932 1951) He treated this patient satisfactorily and controlled her tetany by placing her on a diet of low phosphorus and calcium content In addition he gave her the following medication calcium lactate 10 to 20 gm daily (3 to 6 teaspoonful) to ensure a high calcium intake and to compensate for the calcium poor diet Dihydrotachysterol (A T 10) was given in doses of 2.5 mg (2 capsules of 1.25 mg) daily with Amphojel a proprietary colloidal suspension of aluminum hydroxide The excellent and well maintained biochemical response of the patient and her clinical improvement were striking On various occasions changes were made for investigative purposes in the dosage of dihydrotachysterol It was found that the serum calcium level rapidly fell and tetany developed when dihydrotachysterol with added calcium was withheld Her serum calcium level rapidly returned to normal or above when treatment was reinstituted After 2 years of treatment with dihydrotachysterol, vitamin D in doses of 100 000 units daily was substituted for dihydrotachysterol without significant disturbance in her serum calcium or serum phosphorus levels Calcium and serum phosphorus determinations were made frequently on this patient

The dangers of hypercalcemia cannot be overemphasized Patients may take calcium and vitamin D for years without incident but in some, hypercalcemia may develop rapidly

A patient with carpopedal spasms was given a diet low in phosphorus and calcium content Also given was 150 000 units of vitamin D 15 gm of calcium gluconate and 2 teaspoonsful of Amphojel daily One month later her calcium intake was increased by discontinuing the calcium gluconate and starting the administration of 20 gm of calcium lactate daily She was maintained well and with normal serum calcium concentrations for the next 6 months An acute episode of hypercalcemia was observed 23 months after the institution of treatment with calcium and vitamin D and all antitetany treatment was stopped Her condition improved as her serum calcium level fell Two weeks later treatment was recommenced with the daily administration of 50 000 units of vitamin D and 12 gm of calcium lactate However her serum calcium level rose to 13 1 mg/100 cc in 14 days and therefore all antitetany treatment was suspended for 6 months She is now maintained in a clinically and biochemically normal condition on a diet of low calcium and phosphorus content 20 000 units of vitamin D and 6 gm of calcium lactate daily No reason for this patient s hypercalcemia can be suggested other than that some remaining parathyroid tissue has resumed secretion This supposition is supported by the fact that a small dose of vitamin D is now required to maintain the patient s serum calcium level

Adequate treatment will eliminate acute attacks of tetany, and the chronic complications will not occur The necessity for close control of treatment by frequent serum calcium determinations and for continuing treatment for the rest of the patient s life is stressed

12

Complications during and after Thyroidectomy

TODAY, COMPLICATIONS following thyroid surgery are the exception rather than the rule When they do occur however both the surgeon and the patient become quite disturbed Their uneasiness is justified because the failure to recognize and treat most of these complications may result in death Fortunately in the light of modern knowledge many of these complications can be prevented

The complications following thyroidectomy fall into the following categories

1 Recurrent laryngeal nerve injury
2 Parathyroid removal (tetany)
3 Hemorrhage
4 Tracheal injuries or collapse
5 Cardiac disturbances
6 Air embolism
7 Anesthetic complications
8 Thyroid crisis
9 Noninflammatory edema of the larynx

Careful meticulous surgical technique during a thyroidectomy will in a great measure prevent certain complications Specific reference is made to injury to the laryngeal nerves or removal of the parathyroid glands Both these subjects have been discussed in detail under surgical procedures

Hemorrhage is the infrequent complication of the experienced thyroid surgeon It is however a very grave fear of the occasional operator Most often this bleeding arises from the lateral or median veins These vessels may be friable (especially in the elderly) and are easily torn by blunt dissection or when the surgeon elevates the thyroid lobe Ligation of these veins prior to manipulating the gland will eliminate the possibility of hemorrhage from these vessel The thyroid arteries do not usually bleed after surgery if double ligation is accomplished (cf discussion of arteries under surgical technique)

Postoperative hemorrhage occurring within a few hours after operation is a tragic drama in itself When it develops the patient may become rest

room in satisfactory condition This includes a dry gown for the patient and steam inhalations in the patient's room if it is deemed necessary [141]

Thyroid crisis has been mentioned previously Suffice it to say at this point that proper preoperative preparation of the patient with the antithyroid drugs and iodine should prevent any exacerbation of acute hyperthyroidism or thyroid crisis

Recently patients have been prepared for thyroidectomy with a new type of iodine preparation This iodine is contained in a capsule Each capsule contains 150 mg (two and one half gr) of iodine organically bound and is equivalent in iodine content to 100 minims of organidin solution These capsules are administered 1 a day for 2 weeks prior to operation The glands of those patients prepared with this new capsule were ideal for surgery They were well involuted firm and did not develop any adhesions to adjacent structures The patients themselves did not object to this method of iodinization since they had no iodine taste which is often the complaint when iodine is given in liquid form

Noninflammatory edema of the larynx may be a manifestation of iodism This type of edema may occur following surgery It is usually transitory in type and disappears within 1 week A similar type of noninflammatory edema may occur in myxedema following thyroidectomy The general systemic reaction of myxedema causes the laryngeal edema and is the expression of the generalized complication The correction of the myxedema eliminates the laryngeal edema and this complication evaporates under proper therapy On occasion during the postoperative period noninflammatory edema of the larynx may be confused with laryngeal obstruction However if one remembers that croupy cough stridor wheezing dyspnea and difficulty in breathing are typically manifestations of obstructive laryngeal dyspnea the differential diagnosis can be made

From this discussion on complication during and after thyroidectomy one fact remains in evidence Most complications can be avoided if the surgeon prepares the patient properly for surgery performs a careful thyroidectomy and personally supervises the postoperative management

Immediate Postoperative Care

After thyroidectomy the following is prescribed

1 The patient is given intravenously 5 per cent glucose in water or saline depending upon the age of the patient and whether or not he has lost salt via perspiration
2 Sodium iodide (15 gr) is given in the intravenous glucose
3 An ice collar is placed about the neck for 24 hours This prevents serum accumulation and diminishes edema

less Progressive dyspnea with an associated cyanosis is noted as the fullness of the neck due to the accumulating blood presses on the trachea Dyspnea may be so insidious that the patient passes from a state of anoxemia to unconsciousness very rapidly This type of patient demands immediate assistance The skin clips or silk sutures should be removed and the underlying incarcerated blood clots liberated Blood clots may gush out or may be removed manually The source of the bleeding is detected and controlled with a ligature if necessary This type of bleeding may be more difficult to control than the performing of an entire thyroidectomy

Injury to the trachea is not a very serious complication when compared to postoperative hemorrhage If the trachea is cut several sutures may be used to approximate the laceration A small rent may be covered with a muscle transplant Tracheal collapse is a more serious complication and may occur during or immediately after operation The danger of this complication is in patients with large cervical goiters intrathoracic goiters or retrotracheal goiter (or a combination of all three types) Tracheotomy is a life saving procedure in such cases More specific information on this topic may be found on page 180

Cardiac disturbances may be either cardiac failure or arrhythmia The problem of arrhythmias following thyroidectomy will be discussed subsequently The development of congestive heart failure during or following thyroidectomy should not occur if the patient is prepared properly for thyroidectomy This complication has never occurred in my own experience although such cases have been presented at hospital conference

Air embolism is a rare complication which is seldom seen but which has been discussed by excellent thyroid surgeons Air embolism occur usually when surgery has been completed and the dressing is being applied The patient coughs (often violently) and there follows a noise like air escaping from a tire Cyanosis rapidly occurs and the patient dies immediately It is conjectured that the violent coughing loosens the ligature of a vessel and then air is aspirated [141] When an air embolism occurs the patient's head should be lowered to the floor

In the past anesthesia complications were avoided by the thyroid surgeon by employing superficial nerve block anesthesia In this modern age anesthesia is administered by a competent physican anesthetist No longer should more complications be anticipated in the thyroid patient than in one undergoing a laparotomy At one time cyclopropane anesthesia was used and many patients developed cardiac irregularities Cyclopropane is not commonly used in thyroid surgery today Pneumonia and atelectasis rarely occur when a definite postoperative routine is followed Every surgeon should personally see that his thyroid patient leaves the operating

The presence of auricular fibrillation has been an indication for administering some drug to control the irregularity Digitalis does not possess the property of re establishing normal rhythm in patients who have auricular fibrillation In the 11 patients mentioned quinidine lactate or quinidine sulfate was employed with excellent results If a patient has had an embolic accident quinidine should not be administered When quini

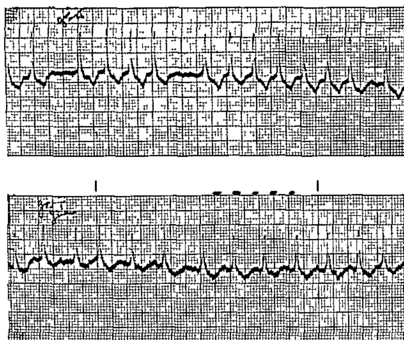


FIG 72 Electrocardiogram of a patient with thyrotoxicosis showing auricular fibrillation (leads I and II) This patient had a preoperative BMR +45 and a total cholesterol of 150 mg per cent This is the commonest type of arrhythmia seen in thyrotoxicosis (The small oscillations are designated 1 waves or fibrillatory waves)

dine lactate is given the same precautions should be taken as when quinidine sulfate is employed for this cardiac arrhythmia The patient must be observed closely and should remain in bed for 2 hours after the last dose of quinidine As soon as the fibrillation is discovered the patient is given quinidine (prescribed by a cardiologist)

The best results seemed to be obtained when the drug was given at an interval of 2 hours between doses On the first day 2 doses of 0 2 Gm were given as a test for hypersensitivity If no symptoms developed 5 doses of 0 4 Gm were given on each of the following days

Since the completion of the survey 6 patients have been seen with

4 Syrup of hydriodic acid (2 dr) is given every 4 hours as soon as the patient can take it orally This is an excellent liquefying expectorant
5 The patient is placed in a sitting position as soon as possible
6 The patient is allowed out of bed and eats a regular diet the day after surgery

A few words of explanation are in order on the use of sodium iodide postoperatively This drug is not given for any reason other than that it is a liquefying expectorant It enables the patient when reacting to eliminate any mucus plug which may accumulate in the respiratory tree Hydriodic acid is given for the same reason during the immediate post operative period

Transient Cardiac Arrhythmia following Thyroidectomy

A purposeful survey was made of 100 consecutive thyroid procedures to determine cardiac arrhythmias Sixty of these patients had primary hyperthyroidism (toxic goiter) Of these only 9 had true hyperthyroid heart disease, determined preoperatively Thus 51 patients with severe hyperthyroidism did not have any cardiac disturbance which was demonstrable prior to operation Following thyroidectomy however 11 of these patients developed cardiac irregularities which were determined by clinical auscultation and corroborated by electrocardiogram The arrhythmia encountered was auricular fibrillation

Disturbance in the rhythm of the heart is a common occurrence in patients with hyperthyroid heart disease However to find auricular fibrillation developing after thyroidectomy in patients without a pre existing arrhythmia is not the usual pattern of events The postoperative presence of auricular fibrillation could not be interpreted as a cyclopropane arrhythmia since this drug was not employed for anesthesia

Although auricular fibrillation may occur in young people as a purely functional disorder it is usually associated with organic heart disease Especially is this true in hypertensive rheumatic and hyperthyroid heart disease Auricular fibrillation is characterized by an absolute irregularity of the heart and the entire absence of an underlying basic rhythm This was the situation with the 11 patients following thyroidectomy

The exact time of onset of this irregularity postoperatively could not be determined However it was noted within 6 and 9 hours following the patient s return from the operating room In all instances the arrhythmia was discovered during evening rounds (about 5 00 or 6 00 P M) on the same day of operation which usually commenced at 8 30 A M

tracheotomy which is never open to dispute is postoperative tracheal obstruction secondary to hemorrhage Emergency tracheotomy in these cases is imperative for the preservation of life Elective tracheotomy following thyroidectomy however presents a different problem The question as to when this procedure is indicated may be open to dispute

An elective tracheotomy is advocated in those patients with large colloid goiters producing tracheal compression and/or marked tracheal deviation This is especially true when there is substernal extension of the gland In the case presented here a fatal factor outcome would have been impossible without an elective tracheotomy When there is a question as to whether or not to perform a tracheotomy and doubt exists I prefer to do the tracheotomy

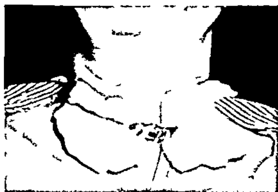


Fig 5 Elective tracheotomy following thyroidectomy for massive substernal colloid goiter

Case report The patient M B 56 years of age was seen in May 1947 He presented the history of a swelling in the neck of ten year duration During the past six months this had increased in size and more recently over a period of several weeks he had developed hoarseness and dyspnea on exertion Because of the hoarseness and dyspnea he was referred for surgical treatment Physical examination at that time revealed an obese man weighing 250 pounds His blood pressure was 190/100 pulse 100 B M R plus 16 The significant findings were referable to the thyroid gland The gland was enlarged to twelve times normal size Preoperative x ray study revealed tracheal deviation to the left and a substernal extension of the thyroid into the mediastinum The patient talked with difficulty and displayed hoarseness which was his chief complaint The patient was prepared for operation and subjected to a total thyroidectomy and elective tracheotomy on May 21 1947 He had an uneventful recovery The tracheotomy tube was removed on the second postoperative day and the patient was discharged from the hospital one week after his operation

As demonstrated by this patient the large thyroid gland displaced the trachea Displacement of this type is conducive to diminution in the exchange capacity of the tracheal airway Such insufficiency may precipitate

auricular fibrillation following thyroidectomy These 6 patients did not receive quinidine or any other drug aimed at arresting the arrhythmia All 6 patients had a disappearance of the auricular fibrillation from 2 to 4 days after thyroidectomy It seems therefore that this type of auricular

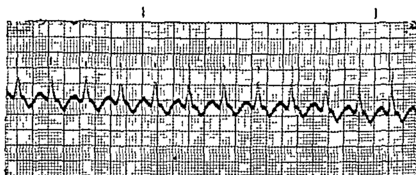


Fig 73

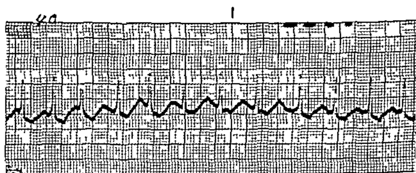


Fig 74

Fig 73 Electrocardiogram of the same patient after the administration of quinidine (8 gr) Changes noted in F waves indicate a slowing of conduction time which is a typical quinidine effect

Fig 74 Electrocardiographic tracing taken 24 hours after the first recording There was no change in rhythm in the tracings taken subsequently on the second and third postoperative days Most cardiac arrhythmias due to thyrotoxicosis disappear spontaneously following thyroidectomy

fibrillation is transient in type functional in origin and does not necessitate specific drug therapy

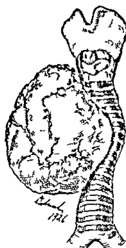
Elective Tracheotomy Following Thyroidectomy

Surgeons who operate on many thyroid patients are frequently confronted with the problem of performing a tracheotomy An indication for

field is obtained and the cervical portions of the thyroid can then be resected easily If the substernal and intrathoracic portion of the goiter cannot be removed easily through the cervical incision then an intrathoracic approach to the goiter must be made Under this circumstance the goiter may be removed in one or more of the following methods

1 Manual removal through the superior thoracic outlet
2 Separation of the sternoclavicular joint





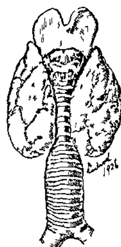


Fig 76 Fig 77 Fig 78

Fig 76 Diagrammatic illustration showing compression of the trachea between two enlarged lobes of the thyroid gland at different levels The trachea is distorted into an S shaped tube with a diminution in caliber at the compression site and dilatation below the obstruction

Fig 77 Tracheal compression secondary to a unilateral thyroid enlargement

Fig 78 Bilateral tracheal compression due to a symmetrical enlargement of the thyroid gland at the same level Beneath the compression site is the characteristic dilatation found below the point of obstruction

3 Division of the manubrium and/or the sternum
4 Thoracotomy especially in goiter plongeant

Manual liberation and removal of an intrathoracic goiter from adjacent mediastinal tissue can be accomplished via digital dissection The index finger is inserted into the mediastinum outside the capsule of the adenomata This procedure is continued around the entire exterior surface of the goiter as far as possible Little bleeding is encountered since this area forms a natural line of cleavage between the goiter the pleura and mediastinal tissue This procedure of digital dissection is the initial step in

anoxia This may increase a previously existing anoxic state which is characteristic of patients with hyperthyroidism Anoxia is further increased if a mucus plug occludes a major or minor bronchus Tracheotomy establishes an artificial airway which eliminates the incipient anoxia

Often large goiters insidiously compress the recurrent laryngeal nerve Following the removal of the offending pathology edema occurs about the site of compression This edema may result in transitory paralysis of one or both vocal cords paralysis disappears when the edema subsides In this instance a tracheotomy is indicated until the edema has subsided

Substernal and Intrathoracic Goiter

Approximately 1 per cent of adenomatous colloid goiters are within the thorax Twenty five per cent of adenomatous goiters are substernal in location An examination of the neck in a patient with a substernal or intrathoracic goiter reveals dilated veins which may extend superiorly and even *inferiorly on to the chest wall The patient usually seeks relief because* of dyspnea Raspy breathing inspiration stridor choking and coughing often suggest the diagnosis before the patient declares his symptomatology Motions of the neck such as sudden flexion or extension or motion to the right or left will produce coughing or choking This is due to compression In extreme situations the trachea may collapse and death may occur before the patient is prepared for surgery When an intrathoracic goiter does not compress any important structures no obvious sign or symptom may be noted The presence of this intrathoracic mass may be visualized only by roentgen examination of the chest

It is not uncommon for the recurrent laryngeal nerve to be under tension or even paralyzed by an intrathoracic goiter When this occurs aphonia may result Complete or partial paralysis of the vocal cords may be produced by the displacement of large cervical blood vessels which is caused by enlargement of an intrathoracic goiter

In addition to the compression resulting from large goiters in the neck tracheal and/or bronchial compression may also result from substernal or intrathoracic goiters Surgery is then necessary to relieve the embarrassed respiration Often substernal and intrathoracic goiters cannot be removed easily through the usual cervical incision When the incision is made one must be aware of the fact that exposure is more important than the cosmetic effect or the plastic result It is well to bear in mind that the best location for the incision is lower than that usually made It should be parallel to a normal flexion crease of the neck The smaller lobe or lobes of the thyroid are usually removed before the superior thyroid vessels are identified and ligated After ligation of the superior thyroid artery a dry

Phantom Goiter

During the past eighteen years and more many private and ward patients with thyroid disturbance have been examined, managed and/or treated. Of all these patients three have made an indelible impression upon me. All three were elderly women with a history quite similar in all three cases.

Their stories were those of large cervical adenomatous goiters of many years duration which were untreated until compression symptoms developed in the neck region. At this stage they were seen by their respective family physicians who prescribed iodine solution. The iodine caused an involution of the thyroid tissue present in the goiter, with a resultant diminution in the size of the goiters. This decrease in size was sufficient to allow the goiters to drop by their own weight behind the sternum or behind the clavicles. The goiters either ceased to be visible completely or diminished in size so that they were no longer prominent. These patients thought that the goiters had disappeared overnight like a phantom spirit.

The facility with which a goiter can gravitate into the chest is understandable when one considers that the adenomatous goiters possessed many areas of cystic degeneration. These areas are readily compressible and hence can pass through an inlet much smaller than the mass itself. The descent of these goitrous masses is deeper behind the sternum than when they are located behind the clavicle. The reason for this is that there is Sibson's aponeurosis behind and above the clavicle, but it is absent behind the manubrium sterni.

Sibson's aponeurosis is (named for Francis Sibson, an English anatomist, 1814–1876) is in reality a vertebropleural ligament attached to the seventh

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Fig 80—Continued

The lower diagram demonstrates tracheal deviation resulting from an intrathoracic adenoma. Digital and manual removal of such an adenoma necessitate its liberation from adjacent tissue as well as the pleura. There is danger here of perforating the parietal pleura. After separating the adenoma from contiguous structures, it can be grasped with thyroid clamps and lifted out of the mediastinum to the level of the clavicle. The top of the adenoma can then be incised and removed (decapitation). The inner contents of the adenoma are thus exposed and found to be soft, indicating an adenomatous colloid goiter. If the mass is hard, it is usually carcinoma and most likely an inoperable lesion. When the mass is found to be soft, it is usually cystic with necrotic tissue which can be crushed easily with the finger and removed with a gallbladder scoop. Suction may also be used. Removal of the interior contents of the adenoma diminishes the size of the goiter markedly. The capsule is then grasped again with thyroid clamps and retracted superiorly out of its bed; further dissection of the exterior aspect of the capsule from contiguous structures will gradually liberate the entire mass. This procedure is satisfactory in most instances and will eliminate the necessity for dividing the sternoclavicular joint.

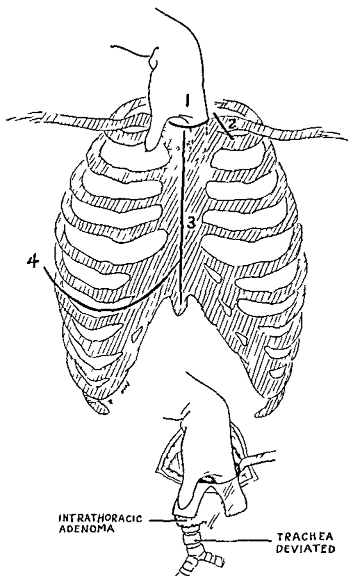


FIG 80 Diagram illustrating the methods of removing substernal and intrathoracic goiters

1 Manual and digital removal through the superior thoracic outlet

2 Separation of the sternoclavicular joint when the goiter is fixed in the superior mediastinum

3 Division of the manubrium and/or the sternum to remove goiters fixed in the anterior middle mediastinum and those which cannot be reached through the superior mediastinum

4 Thoracotomy when the goiter is intrathoracic and appears similar to a pulmonary tumor as in goiter plongeant

Complications of Tracheotomy

The performance of a tracheotomy is not free from hazard A decision not to do a tracheotomy often has been influenced by the fear of com plications These complications may occur as (1) infection (2) emphy ema (3) pulmonary infection or (4) tracheal steno is

Infection Tracheal ecretions emanating from the tracheotomy tube carry organi ms into the operative site This may produce a wound in fection When ilk is u ed for ligatures infection is a serious complication Sep is is diminished if the dre ings are changed every half hour during the first 24 hours Infection can travel sub ternally and produce a medi astinitis As a prophylaxis agaınts this a generous gauze pack is employed to block off the mediastinum Penicillin is given parenterally during the period in which the tracheotomy tube is in situ In some cases the patients develop thick putum which threatens to block off the tracheotomy orifice This is controlled by penicillin inhalation as a supplement to the intra muscular dosage

Emphysema Air e caping about the tracheotomy tube may re ult in emphysema If air accumulates beneath the skin subcutaneous emphysema results Mediastinal emphysema develops when air dissects under the deep cervical fascia In piration produces a normal negative pressure which will increase the spreading power of the air If the media tinal emphysema continues it may reach the pleural cavity cau ing a pneumothorax The best preventive measure against the development of emphy ema is pack ing The wound should be packed widely and left open

Pulmonary Infection The least probable complication is the develop ment of pneumonia or edema Constant attention to the tracheotomy tube with frequent aspirations employing an adequate suction apparatus will prevent the aspiration of mucus which could stimulate an infection or produce an atelectasis If the need arises penicillin can be instilled into the re piratory tree and the tracheotomy tube

Removal of the Tube The trachea is a re ilient organ and readily re turns to its proper anatomic location For this reason a tracheotomy tube is employed for 1 or 2 days 3 days is the longest time The presence of complications however may necessitate leaving the tube in place longer than usual Prior to removing a tracheotomy tube an x ray of the chest should be taken This will demonstrate any fluid accumulation in the sub sternal pace which may be the source of future tracheal compression In the event that the fluid may be old blood no damage is anticipated if the blood is clotted A large blood clot may be identified by placing a stetho scope over the area A friction rub similar to a pericardial friction rub will be heard The presence of this ound indicates that the tube may be

cervical vertebra above and the dome of the pleura below This ligament supports and strengthens the dome of the pleura For this reason a 'falling' or phantom goiter cannot descend too far behind the clavicles because the dome of the pleura plus a supporting structure in the nature of an aponeurosis is present This same aponeurosis can become attenuated over a period of time (years) due to a large goiter pressing on it from above associated with a continual respiratory action of the lung and pleura constantly producing friction against it Physiologic activity of this type inevitably results in an attrition of the structure involved and hence it attenuates Sibson's aponeurosis

Following the surgical removal, therefore of a subclavicular goiter on either the right or left side there results a visible herniation through Sibson's aponeurosis This swelling results from an increase in the expansion of the underlying lung parenchyma which is no longer compressed by an overlying goiter Hence it is that some patients will call attention to this swelling weeks after thyroidectomy An explanation of the pulmonary mechanism will relieve the patient of this anxiety even as it will dispel the impression that the goiter was not removed in toto or that it is recurring so soon after surgery

Tracheotomy and Thyroidectomy

At the time of thyroidectomy tracheotomy is a simple procedure The trachea is cleansed of thyroid tissue and the cartilaginous rings are clearly visible The site of election is usually below the second cartilaginous ring because high tracheotomy may produce laryngeal edema which may result in a stenosis High tracheotomy is more apt to cause perichondritis for the same reason Moreover high tracheotomy results in difficult decannulation For these reasons the fourth cartilaginous ring is the preferred level

A vertical incision is made in the center of the fourth cartilaginous ring with a #15 bladed scalpel This is usually sufficient However on occasion a small segment of cartilage may be removed in order to facilitate the entrance of the tracheotomy tube With the stylette in situ the tracheotomy tube is inserted into the trachea The membraneous portion of the trachea relaxes sufficiently to enable the cartilaginous ring to spread

A plain half inch gauze pack is then placed on either side of the tracheotomy tube The stylette is removed and the tracheotomy is allowed to function on the operating table Anesthesia is generally discontinued at this stage Since patients with substernal goiter are usually given intratracheal anesthesia tracheotomy necessitates the removal of the endotracheal tube

13

Thyroid Cancer

A study of primary carcinoma of the thyroid gland demonstrates that these carcinomata are a heterogeneous group of tumors of markedly different histological structure and biological behavior In addition these carcinomata are relatively uncommon Because of this fact many years passed before there was a sufficient number of recorded cases to make possible a correlation of histological pattern of various thyroid cancers and the clinical course and biological activity of these lesions Until a harmonious relationship was established between the histological picture and the biological activity of thyroid cancer there was much confusion and indecision about the subject of thyroid cancer From the pathological point of view the less anaplastic carcinomata particularly were surrounded by a nebulous uncertainty The benign histological appearance of these anaplastic lesions or their apparently benign course was at variance with the then current concept regarding carcinoma In preceding decades these tumors were treated as benign lesions For this reason the only primary carcinomata recognized were the more anaplastic type The treatment for these lesions at that time was most unsatisfactory In view of this inadequate therapy there was much pessimism regarding the prognosis in patients with thyroid carcinomata As with many other malignant lesions unless there are better diagnostic or therapeutic methods available there is continual doubt that the ultimate results in the treatment of anaplastic thyroid lesions will be improved However management of other types of thyroid cancer with present day therapeutic methods offers a better prognosis to the patient provided of course that the tumor is not inoperable at the time of diagnosis It must be remembered that the present day attitude toward the removal of nodular goiters and all nodules in the thyroid gland will undoubtedly materially reduce the occurrence of thyroid carcinoma It should also reduce the number of patients who will be found to be inoperable as time passes Undoubtedly our increasing knowledge of thyroid cancer will unquestionably contribute to the ultimate better prognosis in patients afflicted with this disease

The pathological classifications of thyroid cancers have been confusing on many occasions From the point of view of therapy the pathological slide is of importance only insofar as it identifies the type of cancer Cope

removed since the blood is solidified If serosanguineous fluid is present it must be aspirated before removing the tracheotomy tube

The procedure employed prior to the removal of the tube is to defunctionalize the tracheotomy This is done simply by inserting the stylette into the tracheotomy tube so that it is functionless If the patient can tolerate this occlusion for 12 hours it is safe to remove the tracheotomy tube The tube should be removed only when the possibility of any complication has been eliminated

Tracheal Stenosis Cicatricial tracheal stenosis may be a delayed complication following tracheotomy This complication may result from a high tracheotomy a malfitting cannula or infection The stenosis results from erosion of the tracheal mucosa, perichondritis and chondral necrosis The subsequent cicatrix produces varying degrees of stenosis and leads to respiratory difficulty This complication may be avoided by performing a tracheotomy below the second ring of the trachea at least An adequate cannula fitting comfortably in situ and the combating of infections with the various antibiotics are further prophylactic measures which can prevent cicatricial tracheal stenosis Formerly, the treatment of cicatricial stenosis of the larynx and trachea was extremely difficult The result was that the patient often was compelled to accept permanent tracheotomy continuous respiratory disability and even death However at the present time the following methods are now available for the relief of this distressing stenosis

1 Endoscopic dilatation
2 Laryngostomy or tracheostomy with incision or excision of the scar and insertion of a dilator or a free skin graft on a mold of plastic sponge
3 Resection of the larynx or trachea with immediate anastomosis
4 Resection of the trachea or bronchus with reconstruction

lary cancers are slow growing but metastasize early to the lymph nodes where the tumor may remain for months or years Since they invade slowly and remain in the lymph nodes for a long time radical surgery offers a good prognosis



FIG 89 Microscopic section showing papillary cystadenocarcinoma of the thyroid

3 A hybrid type of thyroid cancer often called benign metastasizing goiter or metastasizing adenoma has been mentioned in the literature The primary thyroid lesion appears to be benign but distant metastases may occur in the bones (it avoids the lungs) This type has been reported in the later decades of life Hurthle cell adenomata may belong to this group

Cope of Boston has called attention to a node which appears in the neck either as a complication to malignant disease or in thyroiditis[87] This node may be felt on the trachea just above the thyroid isthmus The presence of this node is consistently indicative of these conditions so much so that Cope has called it the Delphian node after the classical oracle at Delphi

has suggested that what really concerns us in the treatment of cancer is the biological behavior of the tumors [87] This seems to be a very rational approach to the problem

A survey of thyroid cancer from the biological point of view collects these cancers into three groups

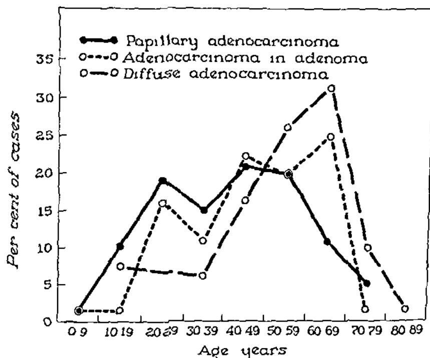


Fig 81 Age distribution of carcinoma of the thyroid gland The occurrence of papillary lesions in children and young adults is not unusual However contrary to erroneous impressions the age distribution of carcinoma of the thyroid is not greatly different from that of carcinomata elsewhere in the human body (Courtesy of the Mayo Clinic Pemberton J and Black B M Cancer of the thyroid American Cancer Society Bulletin 1954)

1 Thyroid cancer similar to that seen elsewhere in the human body i e a disease of the middle age and the geriatric group In this group are found the undifferentiated cancers and adenocarcinomas
2 The commonest form of thyroid malignancy is papillary adenocarcinoma These cancers of the thyroid are encountered in children and adults and are distributed equally in all decades of life They are no more malignant in children than in adults The papil



Fig. 84 Carcinoma of the thyroid gland displacing the trachea to the left (T). C, [illegible] enlarged cervical lymph nodes resulting from regional metastases. (Graham, E. A.: Surgical Diagnosis, Philadelphia, W. B. Saunders Co., 1930.)

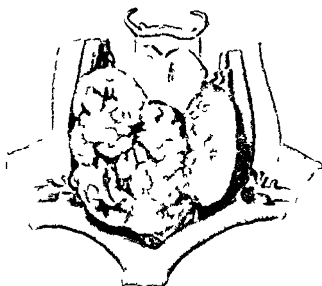


Fig. 85 Anatomic representation of carcinoma of the thyroid gland. (From Pfizer *Spectrum* appearing in the J. A. M. A.)

At times a Delphian node is difficult to distinguish from a pyramidal lobe In such situations hyperextension of the neck is helpful in determining whether the node is attached to the thyroid gland If it is attached to the gland it will rise above the thyroid when the neck is hyperextended

The Delphian or sub Delphian nodes (may be one or several) are the first to be exposed at the time of operation They are usually found anterior to the larynx and the trachea It should be remembered that this



FIG 83 Roentgenogram showing a meta tatic area in the bones of the skull from a so-called benign metasta izing adenoma of the thyroid This le ion is con idered a hybrid type of thyroid cancer becau e it appears benign in the original tumor but metastasizes to bone

lymph node is often found enca ed in the cervical fascia in the midline just above the thyroid isthmus anterior to the lower portion of the thyroid cartilage When this gland or glands are seen they are the first ones encountered Examination of these nodes histologically will foretell the nature of the disease process to be found in the thyroid gland

The Delphian node receives lymph from the upper anterior portion of the body of both lobes and from the upper poles and the i thmus Cancer originating in any of the e areas has been found to metastasize to this node or nodes Only one exception pertains to this ituation namely, that

nongoitrous region It appeared that the majority of cancers of the thyroid arose in long standing nodular goiter

At the present time there is no exact certitude concerning this etiological relationship It may well be that the malignant lesions do arise in preexisting benign adenomata However the pathological evidence in support of this belief is not voluminous The histological picture of a localized area in which malignant change has occurred in an otherwise benign adenoma is not a common finding The usual picture is for an encapsulated nodule to be either entirely benign or entirely malignant throughout Pemberton[3 3 374] has reported that the proportion of carci-

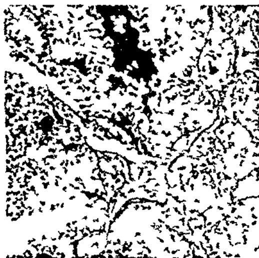


Fig 87 Microscopic section taken from the gross specimen pictured in figure 86 The pathologic picture of this section is that of adenocarcinoma

nomas that arise in preexisting goiters is far smaller at the present time than was reported in previous years

The sequence of events concerning a benign adenoma going on to the carcinoma phase is not postulated to account for the apparent development of carcinoma in a nodular goiter Clinical experience unfolds the fact that the less anaplastic carcinomata especially the papillary lesions and the great majority of malignant adenomas increase in size at a very slow pace Our knowledge based upon statistical study clearly demonstrates that these lesions can exist for years without causing local symptoms and without giving rise to metastasis In such patients until the metastasis spreads the lesions are considered to be clinically benign Conversely a thyroid nodule known to be present for many years when re-

since the node also receives lymph from the larynx a carcinomatous metastasis in this node or group of nodes is not necessarily pathognomonic of cancer arising in the thyroid gland However at operation additional examination of the thyroid will substantiate the diagnosis of thyroid cancer



FIG 86 Gross specimen of primary thyroid carcinoma showing the appearance of the gland on cross section Microscopically the lesion was identified as a papilliform type of adenocarcinoma (Rice L W Histology of the thyroid gland Medicine Illustrated Feb 1949)

Nodular Goiter and Carcinoma

The consensus among the majority of authorities appears to indicate that a pre existing benign adenoma (especially a fetal adenoma) may be the precursor of carcinoma in the thyroid gland[3 3 3 8 411] The relationship between the two lesions was thought to be such that an adenoma was in fact a precancerous lesion The evidence in support of this thought was based upon clinical experience in the majority of instances Carcinomata were relatively common in those geographical areas where adenomatous goiter was endemic On the other hand it was relatively uncommon in the

nongoitrous region. It appeared that the majority of cancers of the thyroid arose in long standing nodular goiters.

At the present time there is no exact certitude concerning this etiological relationship. It may well be that the malignant lesions do arise in preexisting benign adenomata. However the pathological evidence in support of this belief is not voluminous. The histological picture of a localized area in which malignant change has occurred in an otherwise benign adenoma is not a common finding. The usual picture is for an encapsulated nodule to be either entirely benign or entirely malignant throughout. Pemberton[4, 7, 174] has reported that the proportion of carci-

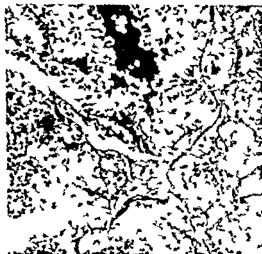


Fig. 87. Microscopic section taken from the gross specimen pictured in figure 86. The pathologic picture of this section is that of adenocarcinoma.

nomas that arise in preexisting goiters is far smaller at the present time than was reported in previous years.

The sequence of events concerning a benign adenoma going on to the carcinoma phase is not postulated to account for the apparent development of carcinoma in a nodular goiter. Clinical experience unfolds the fact that the less anaplastic carcinomata, especially the papillary lesions, and the great majority of malignant adenomas increase in size at a very slow pace. Our knowledge based upon statistical study clearly demonstrates that these lesions can exist for years without causing local symptoms and without giving rise to metastasis. In such patients until the metastasis spreads the lesions are considered to be clinically benign. Conversely, a thyroid nodule known to be present for many years when re-

moved at operation is found to be unrelated to carcinoma By this is meant that the carcinoma develops in the extranodular tissue and infiltrates or engulfs the unchanged benign nodule It is quite probable that some carcinomata develop in pre-existing benign adenomata The exact proportion of cases in which this occurs cannot be stated dogmatically[33, 34] It cannot be denied that very many malignant thyroid lesions are malignant from the time that they are first revealed as nodules in the thyroid gland For this reason the *prophylactic concept of preventing the development* of carcinoma by the removal of benign adenomata has both its an



Fig 88 *Microscopic section of primary oat-cell type of thyroid carcinoma* The cells have a spindle form which easily confuses the pathologist This type of carcinoma must especially be distinguished from fibrosarcoma and Riedel's struma (Price L W Histology of the thyroid gland Medicine Illustrated Feb 1949)

tagonists and advocates It should not be implied however that nodular goiters should be allowed to remain since it is known that carcinoma is found often enough in nodular goiters to suggest a relationship between the two

Unfortunately the symptoms and signs of thyroid cancer except for the possibility of a thyroid nodule develop quite late in the course of the disease A common experience is for the diagnosis to be suspected only when the lesion has metastasized or has broken through the confines of the thyroid gland As is well known according to the present day concepts of malignant lesions the interval between the development of cancer and its spread is the period during which treatment has the best chance of overcoming the progress of the disease Unfortunately, in the majority

of patients with thyroid carcinoma this interval between development and spread is quite long. Thus it can be understood that the betterment of prognosis lies in the removal of the malignant thyroid nodule before it



Fig 89 Roentgenogram of the lower spine (patient complained of low back pain) showing early metastasis in the lumbar vertebra from a known carcinoma of the thyroid

has spread This implies that nontoxic nodular goiters should be removed almost routinely

Although the exact incidence of carcinoma in nodular goiter is not known there is sufficient information concerning its incidence in those that have been removed surgically This incidence in surgical material as reported in the literature varies from 4 to 8 per cent[3 9 363 365 367 3 0 3 6] During the ten year period from 1938 to 1947 the incidence of carcinoma in resected nodular goiters was 4 8 per cent at the Mayo Clinic[3 3] The

term "nodular goiter" is used at the Mayo Clinic to designate all goiters including *clinically evident carcinomas* that were nodular on clinical examination

The diversity of the histological architecture of thyroid cancer and its variation in biological behavior have made pathological classification quite difficult Many years ago there were many complex classifications of thyroid cancer so that in most instances the tabulations were most unsatisfactory A simpler modern classification is much more preferable

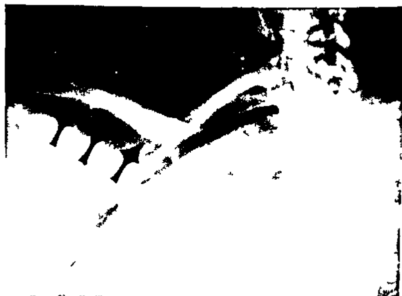


Fig 90 Roentgenogram of clavicle demonstrating moth-eaten appearance of the inferior margins of the bone due to metastase The patient was a 35 year old housewife with proven cancer of the thyroid gland

Although renowned for their elucidation of the thyroid cancer problem its classification seems to differ among the various large clinics and groups One of the most satisfactory classifications is that used at the Mayo Clinic This grouping has been found adequate for the proper classification of primary malignant tumors of the thyroid gland These lesions are grouped as follows

1 Papillary adenocarcinoma
2 Adenocarcinoma in an adenoma (malignant adenoma)
3 Anaplastic adenocarcinoma
4 Epithelioma
5 Sarcoma



Fig 91 Chest roentgenogram of a female with cancer of the thyroid and pulmonary tuberculosis This patient had a moderate swelling of the thyroid gland with tracheal compression (Histologic section confirmed the diagnosis of thyroid cancer) This x ray film shows that a thoracoplasty was performed Posterior portions of the upper six ribs on the right side are missing with a moderate collapse of the thorax and incipient regeneration of the resected bones noted Numerous healed calcific lesions are present in both upper halves of the chest No evidence of bone or pulmonary metastases in this chest film is recorded This illustration is presented as a problem in differential diagnosis between pulmonary tuberculosis and pulmonary metastase

Treatment of Thyroid Cancer

The treatment of thyroid cancer is radical It includes surgery high voltage radiation or radioactive iodine A combination of these three methods may be the usual therapeutic regimen Hormonal therapy has

not been established as an accepted method of therapy Of all the therapeutic modalities available one can state that the treatment of cancer of the thyroid is primarily surgical Irradiation is of secondary importance

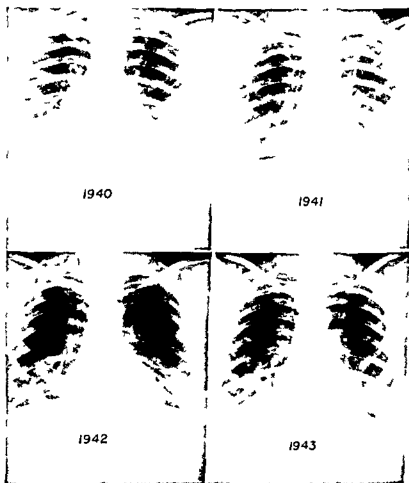


Fig 92 Serial chest films of a 45 year old housewife with pulmonary metastases from thyroid carcinoma The metastases were detected in 1940 This series shows the progress of the disease with yearly interval x ray examinations until he died in 1951 The last film shows a pleural effusion secondary to carcinomatosis

This series of films is continued on page 195-19

finding its greatest utility in those patients in whom all the malignant tissue cannot be resected The extent and type of operation is governed by the extent and the type of the local spread of the carcinoma The idea of radical removal of the primary lesion together with the tributary lymphatics en masse is not particularly applicable to the carcinomatous lesions

of the thyroid because of the anatomical relationship of this gland to the contiguous vital structures. Moreover there is much evidence to support the belief that radical dissection in the presence of certain neoplastic

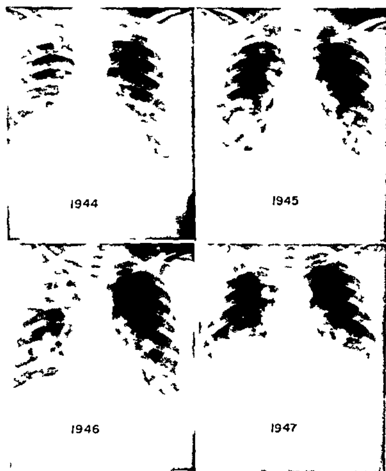


Fig 92—continued

lesions is needless whereas in other types of lesions such radical dissections are entirely useless [61]

Palliative Resection

In the treatment of thyroid cancer palliative surgical procedures have a most useful place. Prior to surgery it is almost impossible to determine the resectability of all but a lesion in the advanced stages. If at the time

of surgery the lesion proves to be inoperable locally, the surgeon should, nevertheless try to remove as much of the malignant tissue as possible The tissue that remains can be treated by radiation, by the implantation of radon seeds etc Moreover postoperative external irradiation is usually

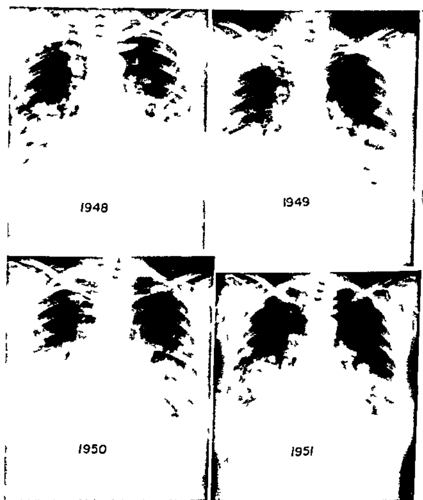


Fig 92—*continued*

more effective after the resection of a large portion of the malignant tissue since the treatment can then be limited to smaller areas

In some patients with advanced carcinoma the surgeon is restricted as to the amount of resection Under this circumstance he may only be able to perform a biopsy and/or establish an airway It is mandatory for the surgeon however, to attempt to free the trachea from the carcinomatous mass at the time of surgical exploration The establishment and main

tenance of an airway are among the principal end results of palliative operative procedures.

Tracheotomy may be a life-saving procedure in patients with thyroid cancer. For this reason it should be considered in any case in which an extensive dissection is performed in the area of the larynx and the trachea. Tracheotomy should be performed especially where large masses of malignant tissue cannot be removed and must remain in the neck. It is also advisable to perform a tracheotomy when irradiation is planned following surgery. The optimum time for performing a tracheotomy is when the patient is in the operating room for the original palliative procedure. For it is at this time that it is safer and easier to perform. As the disease progresses a patient with thyroid cancer will develop tracheal obstruction.



FIG 92—*continued*

When this stage is reached any attempt to find and to open the trachea in the presence of recurring carcinoma is not only extremely dangerous but is technically most difficult. On occasion it may be necessary to pass a bronchoscope to maintain an airway while the surgeon tries to dissect away carcinomatous tissue to find the distorted and displaced trachea for a tracheotomy.

On occasion the question of performing a gastrostomy is raised. It is rarely necessary to perform this procedure in patients with thyroid carcinoma because unfortunately the patient dies before a complete esophageal obstruction results.

Radiation Therapy

External Irradiation. Although external irradiation has been used for many years in the treatment of thyroid cancer it is difficult to find un-

of surgery the lesion proves to be inoperable locally the surgeon should, nevertheless try to remove as much of the malignant tissue as possible The tissue that remains can be treated by radiation, by the implantation of radon seeds, etc Moreover postoperative external irradiation is usually

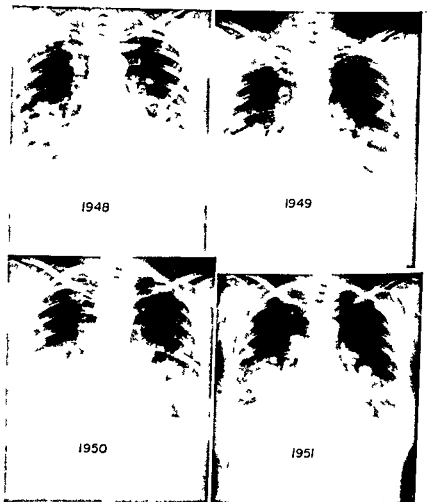


Fig 92—*continued*

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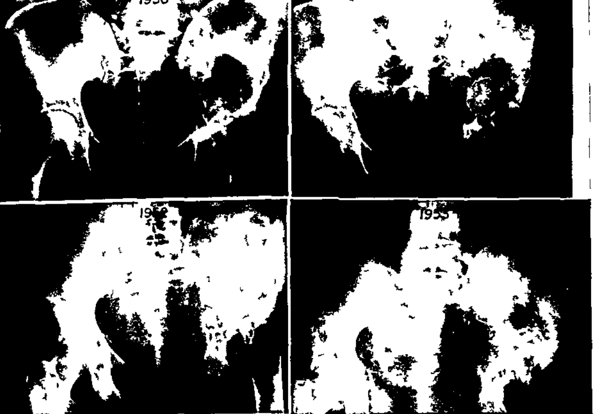


FIG 93 Serial roentgenograms showing metastases to the left pelvis arising from thyroid carcinoma. The patient was seen for the first time in 1944 and died in 1953. This series demonstrates the progression of the lesion from year to year excepting 1946 and 1947. In 1944 the metastasis was found in the left ilium. A gradual inferior extension of the disease is noted to involve the pubic and ischial bones. With the advancement of the disease *the head of the femur is seen to erode through the acetabulum*. Clinically the patient became a gradual cripple as the process advanced. She finally was completely bed ridden until her death.


1945


1949


1944


1948

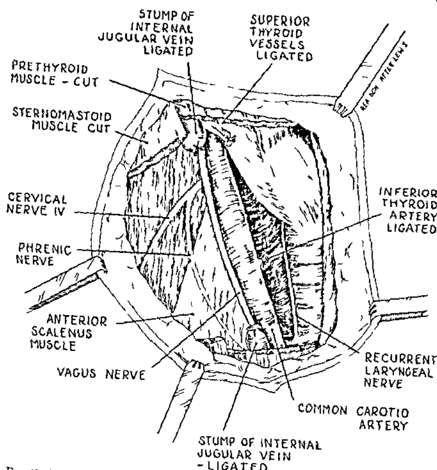


FIG 95 Anatomi relation by atter one l be an l the isthmus of the thyroid have be n removed Malignan y in an adenom penetrated the cap ule of the le ion involving the paren hyma of th gland After the diagnosis i e tabl hed by frozen section of the adenoma it is adv able to arry the inci ion across the neck (hockey stick inci ion) and r move th oppo ite lobe of the thyroid Frequently a micro copic adenoma is present in the lobe oppo it the lesion and may be overlooked at surgery

Sin e thyroid cancer doe inside vein it is a good practice (even for malignant adenoma with inv sion out ide the capsule) to do a radical neck di section with removal of th int rnal jugular vein and the sternocleidoma toid mu cle An adequate neck di ection i an the removal of the sternocleidoma toid mu cle the tributary vein with the int rnal jugular regional lymph no les the thyroid gland and the pre thyroid mu l

Although ancer may b found in only one lobe on macro copic examination it is preferabl t r all thyroid tissue Since thyroid cancer spread via va cular and lymph ti l ann l it is po ible for thyroid cancer to travel from one ide of the neck to th th through lecu ated channels It is for thi rea on that a total thyroid ectomy i done for a unilateral adenomatous lesion

unanimity of opinion as to its effectiveness. Pemberton has collected statistical evidence indicating that the survival rates are somewhat better in those patients who have had resection plus irradiation than in those who had surgical resection alone. It was not so long ago that most radiologists believed that irradiation not only decreased the rate of thyroid cancer growth but actually diminished the size of the lesions. Today there is less certainty as to the efficacy of irradiation. The improvement following



Fig 94 The long incision to be made for the radical removal of the thyroid lobe for cancer in the gland. With this incision it is practicable to remove the sternocleidomastoid muscle, the internal jugular vein, the thyroid veins and lymph nodes.

irradiation is usually temporary, limited and often merely palliative. Some authorities do not even recommend irradiation postoperatively in those cases in which all known carcinomatous tissue has been removed. The author's personal preference is to employ combined surgery and irradiation in patients with *thyroid cancer*.

Of a certainty, in those cases in which the primary lesion cannot be removed completely, external irradiation is advisable. The end results of irradiation treatment for papillary lesions and malignant adenomata are most difficult to evaluate. As a general statement it can be said that if a

neoplastic lesion of the thyroid resembles lymphomatoid lesions the response to irradiation is better than in those tumors which demonstrate larger cells, giant cells or cells resembling fibrosarcoma This latter group is usually not affected by external irradiation

Interstitial Irradiation In order to treat small masses of nonresectable

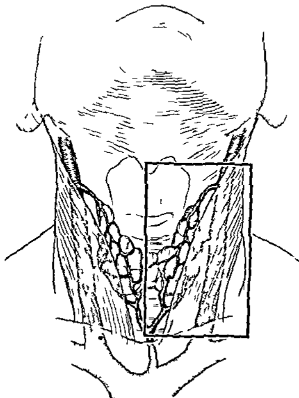


Fig 96 Diagram showing the block of tissue to be removed in patients with carcinoma of the thyroid gland This block includes the sternocleidomastoid muscle the internal jugular vein with all of its tributaries entering the thyroid gland all the lymph nodes and all the thyroid tissue bilaterally (Lahey F H and Ficarra B J Lateral aberrant thyroid Surg Gynec & Obst 82 705–711 1946)

carcinomata one may employ radium needles or radon seeds This method of therapy is not offered as a curative process However prolonged survivals after treatment with radium needles or radon seeds can be attributed to a slower progression of the lesion Irradiation of metastatic lesions not in the neck region is a useless procedure

Radioactive Iodine A new modality of therapy is now available for the treatment of thyroid carcinoma in radioactive iodine This isotope has a limited though definite place in the treatment of certain cases of thyroid

carcinoma It is not the method of choice for the treatment of those lesions which can be removed surgically Radioactive iodine is an available adjunct in the management of inoperable extensions or metastatic growths Its efficacy depends upon the ability of the malignant tissue to concentrate an adequate amount of radioactive iodine Unfortunately some malignant thyroid lesions will not concentrate an adequate amount It may be necessary to stimulate this function before treatment is possible In any case the thyroid gland must be removed totally or destroyed by means of radioactive iodine before the malignant metastatic tissue can be treated

For this reason certain lesions cannot be treated with the isotope because they cannot be stimulated to concentrate radioactive iodine Among those lesions which fall into this category are

1 All anaplastic lesions
2 Hurthle cell type of malignant adenoma
3 Papillary lesions with no follicular component
4 Malignant adenomas composed of solid sheets of cells without follicles or colloid

On the other hand some types of thyroid carcinoma can be treated by isotopic irradiation and with such good possibilities that attempts should be made to use radioactive iodine Stated in a different way there appears to be a definite correlation between the presence of follicles (histologically) and the function of concentrating iodine The probability that a thyroid carcinoma can be treated satisfactorily with radioactive iodine can at times be prognosticated therefore from the cytoarchitecture of the lesion as revealed by the microscope

A determination by surgical exploration that the lesion is either resectable or not resectable is therefore the initial step in the management of a thyroid carcinoma patient At the time of operation all or as much malignant tissue as possible should be removed If the pathological picture of the removed thyroid cancer is such that there is a possibility of stimulating radioactive iodine uptake then total thyroidectomy should be performed On the other hand if the lesion is not operable because of extension it may still be possible to remove all or almost all of the uninvolved thyroid In any event the surgeon should remove as much of the thyroid gland as possible When surgical removal is not possible the thyroid gland must be destroyed by radioactive iodine Surgical removal is far superior to destruction by radioactive iodine however Although the exact reasons are not clear it must be recalled that surgical removal extirpates all thyroid tissue whereas radioactive iodine apparently destroys the follicular elements leaving behind a cadaveric gland which may still possess a hormonal function

Following the destruction of the thyroid gland the patient is given an

antithyroid drug which does not contain iodide This drug may be administered for 3 months or more The object in view is to produce complete myxedema The presence of myxedema initiates the secretion of the thyroid stimulating hormone which acts to stimulate the iodine trapping function of the lesion to be treated When the myxedema is clinically in evidence the administration of the antithyroid drug is discontinued Forty eight hours later the iodine concentrating function of the metastatic lesion is determined by means of a tracer dose of radioactive iodine An ade

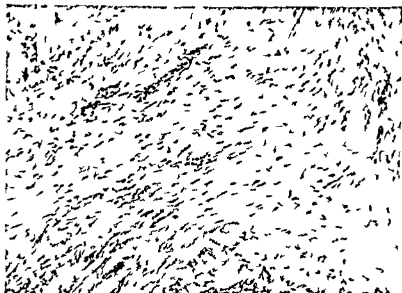


Fig 97 Photomicrograph showing complete destruction of thyroid tissue with radioactive iodine The parenchyma has been replaced by fibrous tissue This type of destruction of malignant tissue is possible if the lesion can be made to concentrate a sufficient amount of radioactive iodine (Pemberton J and Black B M Cancer of the thyroid American Cancer Society Bulletin 1951)

quate uptake as evaluated by the Geiger counter and urinary excretion is determined If the results are satisfactory a massive dose of radioactive iodine is then given This procedure is continued until there is no longer any uptake or until the patient has received the maximum dose possible The administration of radioactive iodine is an individualized problem The duration of treatment and the amount to be administered is determined by the radiologist in conjunction with a physicist The ultimate results of treatment by radioactive iodine cannot be accurately evaluated at this time It is known however that many metastatic lesions have been destroyed and that prolonged survival without evidence of the disease

can be attributed to the isotope. In many cases treatment is unsuccessful because the metastatic lesions cannot concentrate iodine.

Many years ago the distinguished Italian surgeon R. Alessandri read an interesting paper before the Clinical Congress of the American College of Surgeons (Montreal, October 1926). The title of this discourse was "Thyroid and Parathyroid Bone Tumors without Primary Lesion of the Thyroid Gland." At this lecture he reported cases in which he believed that carcinoma developed in accessory thyroid or embryonal aberrations located in osseous tissue. He postulated his hypothesis on the type of bone lesion without primary thyroid carcinoma in the neck. To quote Professor Alessandri: "I do not wish to examine further these two hypotheses, but rather to consider the question of progressive and invading osseous thyroid tumors with secondary metastases and every evidence of malignancy but without a primary malignant tumor of the thyroid gland. Do they really exist or are the related cases simply errors resulting from excessive haste in reporting the case or incomplete study of patients?"

It is difficult to believe that primary thyroid cancer is found in bone. A more logical hypothesis would be that the bone lesions are metastatic lesions originating in the thyroid gland itself. Perhaps the primary lesion went undetected until the metastases occurred. Surgical removal of the thyroid gland in the cases reported may have identified thyroid carcinoma in the neck.

Thytropar following Thyroidectomy for Cancer

The use of Thytropar (TSH) following thyroidectomy for carcinoma has been advocated by some investigators.[4]

Thytropar may be used in the management of postoperative thyroidectomy for carcinoma (1) to indicate the need of further I^{131} therapy and (2) to increase the uptake of therapeutic doses of I^{131}.

In one method of management if there is more than 30 per cent uptake of a tracer I^{131} dose after 8 daily 10 U doses of Thytropar then a therapeutic dose of I^{131} is indicated. Fewer doses of TSH will also increase the uptake of I^{131}. If TSH does not cause this increase in the I^{131} uptake the patient probably does not require I^{131} therapy at that time. Later follow up with the same procedure at a 4–6 month interval may indicate that further I^{131} therapy is needed.

The initial TSH is administered after a tracer I^{131} dose is given about 12–18 hours after the last TSH dose. I^{131} uptake is determined 24 hours after the tracer dose of I^{131}.

This method of therapy entails the use of desiccated thyroid in the postoperative patient in order to maintain a euthyroid state. Endogenous

TSH production is thereby depressed The use of thyroid medication does not interfere with the effect of the exogenously administered TSH

Dosage and Administration Thytropar is administered by intramuscular or subcutaneous injection after dissolving the powder in 2 to 3 cc of physiologic saline solution The following dosage suggestions are based on investigative data and clinical experience

1 In the differential diagnosis of primary thyroid from pituitary myxedema A single dose of 10 U S P units intramuscularly will effect a consistent elevation of the serum protein bound iodine level in pituitary myxedema but will fail to do so in primary thyroid myxedema
2 In functioning metastatic thyroid carcinoma A single intramuscular dose of 10 U S P units effects a significant increase in the thyroid uptake of radioactive iodine (I^{131})
3 In acute thyroiditis 10 U S P units intramuscularly daily for 3 to 5 days

Caution If pituitary myxedema is suspected Thytropar should be administered with the same care that would be exercised in using thyroid extract to prevent precipitation of adrenal cortical insufficiency It is supplied as a sterile lyophilized powder in single 6 cc vials containing 10 U S P units of thyrotropic activity per vial

Thytropar is commercially prepared thyroid stimulating hormone (TSH) It is a highly purified lyophilized thyrotropic principle of bovine anterior pituitary glands In a dry state it is stable indefinitely at room temperature It dissolves readily in physiologic saline solution and when refrigerated retains its potency in solution for at least 4 days

In addition to its being used to increase the concentration of therapeutic doses of radioactive iodine within metastatic thyroid carcinoma it may be employed as follows

1 As an aid in the differential diagnosis between primary thyroid myxedema and pituitary myxedema
2 For the symptomatic relief and ancillary treatment in acute thyroiditis (acute diffuse thyroiditis, acute nonsuppurative thyroiditis subacute thyroiditis)

Addenda

Our present knowledge of cancer is changing from the concepts held not too many years ago One aspect of the cancer problem however has not changed since the thundering herd days of Virchow namely that carcinoma can be disseminated by the surgeon himself More specifically a papillary carcinoma of the thyroid gland if treated gently by the surgeon

may not give the patient too much trouble However if a papillary carcinoma is mishandled (if it is squeezed or broken) then it can become a mechanically induced metastatic disease When a papillary carcinoma of the thyroid has been disturbed and or disseminated via the surgical procedure it may become so erratic that no surgical means however radical can be of any assistance

The best means of handling a patient with this disease is often a highly speculative one if the reader takes seriously the various reports in the world literature There are very few authorities who are in accord with one another and it behooves us to know how and why to do the procedure of choice The lack of uniformity of opinion has resulted in the type of confusion that leaves the general surgeon open to both criticism and malpractice liability For this reason a definite plan of treatment must be established and accepted for better or for worse

The consensus seems to be that when discussing thyroid cancer the following factors should be our guide

1 In almost all cancers of the thyroid gland (excepting rare tumors) the zone of metastasis is central and medial The most frequently involved nodes therefore are those of the superior mediastinum and the lymphatic chain found behind the thyroid gland and along the trachea and esophagus Since these nodes lie in close proximity to most vital structures they must be dissected meticulously and cannot be removed in the *en bloc* dissection advocated by many specialists in this field (This thought must be considered seriously when a radical neck dissection is advocated) By the same reasoning it is not logical to insist upon an *en bloc* dissection of the secondarily involved lymph nodes

2 The cause of death in patients with a papillary adenocarcinoma is not found in the metastases but rather in the compression of vital structures in the neck secondary to medial and central metastases Thus the central area of the neck is the battle ground where victory or defeat is to be found

3 Radical neck surgery with removal of the sternocleidomastoideus muscle in a young girl should not be advocated too strongly because this muscle is very important to the cosmetic appearance of the young girl and the Courts of Law do not uphold this procedure since there are so many well regarded authorities who do not advocate radical surgery of this type for papillary adenocarcinoma In addition the radical surgery often injures the eleventh nerve and this may result in additional complications such as a shoulder drop and secondary arthritic changes

4 The changing concept of the biological activity of thyroid cancer has made us wonder if papillary adenocarcinoma of the thyroid gland can be treated satisfactorily by means of a noncontinuous dissection of the

neck. The involved glands, with preservation of the muscular elements of the neck, will preserve its anatomical appearance.[6, 4]

5. It has been found that many low grade tumors of the thyroid (with malignant changes) may regress if a sufficient quantity of thyroid extract is given to suppress the thyroid stimulating hormone of the pituitary gland.

6. Thought must be given to the fact that a thyroid cancer may contain two or more elements of different tumors. These are similar to mixed tumors. This is especially true in patients under 35 years of age. The most commonly seen mixture in tumors of the thyroid is follicular carcinoma with papillary adenocarcinoma. The biological activity of these tumors approximates the papillary type although histologically the appearance resembles the follicular carcinoma much more architecturally.

7. The prognosis in patients with papillary adenocarcinoma is good, some patients having survived 15 and some 20 years. The routine use of desiccated thyroid (3 gr. daily) may be a factor in the favorable prognosis. Crile believes that papillary adenocarcinoma of the thyroid gland is dependent upon the thyrotropic hormone and that in many cases it is a reversible disease that resembles endometriosis more closely than autonomous cancer. He also believes that a surgeon should think carefully before advocating a mutilating neck dissection for a disease that can be as well controlled by a less radical procedure that preserves the function and contour of the neck.[6, 4]

Conclusions on Treatment

1. Given a patient with hyperthyroidism (without evidence of cancer) three methods of therapy are available. These methods are radioactive iodine, antithyroid drugs, or surgery.

2. Radioactive iodine therapy is the simplest method for the patient. Its greatest disadvantage is the possibility of late carcinogenesis.

3. Antithyroid drug therapy is simple for the patient. Its greatest disadvantages are prolonged administration of the drug, a high recurrence rate when the drug is stopped, and the danger of carcinogenesis.

4. Surgery is still the time tried standard of bringing prompt relief. Moreover, surgery enables the pathologist to identify properly the underlying disease.

5. The rapidly falling morbidity and mortality following thyroidectomy eliminate the objections to surgery in a great measure. Surgery permits the establishment of the presence of cancer and enables radical therapy to be instituted immediately.

6. Thyroid cancer is treated by surgery, radiation therapy, and/or radioactive iodine. In some cases all three methods may be employed.

7. Surgery is the oldest and most commonly used therapeutic method

High voltage radiation is an ancillary supplement and is palliative in the undifferentiated cancers. Radioactive iodine is most effective in two forms of cancer: (a) The differentiated adenocarcinoma. (b) The differentiated metastasizing adenoma. (In the original lesion it often appears benign.)

Persistent and Recurrent Thyroid Diseases

On occasion a patient is subjected to active surgical therapy for the treatment of certain pathologic condition of the thyroid gland without obtaining the desired effect. Although the therapeutic method may have been well planned and executed with dexterity, the end result may not be as satisfactory as the surgeon and the patient anticipated and desired. If the failure to secure the desired result is manifested immediately after the cessation of treatment, the term persistent may be used to describe the clinical picture. If, on the other hand, the symptoms or signs return any time after the immediate postoperative period, it is proper to label that state as recurrent thyroid disease.

The persistence or recurrence of symptoms is most frequently seen in primary hyperthyroidism and cancer. This distressing state may occur even though the patient has been subjected to what apparently was considered to be an adequate thyroidectomy. It has been the sad experience of many surgeons to find that a persistence and even an aggravation of toxic symptoms has occurred following surgery. This type of patient is best treated by postoperative radioactive iodine, with repeated surgery reserved for those individuals who develop thyroid nodules in the neck. Any nodule present or recurrent after thyroidectomy should be removed surgically.

In those instances in which a patient has had a total or subtotal thyroidectomy for adenomatous goiter, a recurrence of a mass in the neck due to thyroid tissue should mean additional surgical removal. In simple adenoma, recurrence may be in reality a persistence and growth of a previous small—even microscopic—adenoma which was overlooked at the time of surgery. For this reason, when a simple unilateral adenoma is found, the opposite lobe should be removed as well as the involved lobe even though no adenoma is visible or palpable. It has also been the sad experience of many surgeons to see a large adenomatous goiter extend substernally with tracheal compression within 2 years after hemithyroidectomy for an apparently solitary adenoma.

Recurrence of symptoms in patients operated upon for thyroiditis is not usual. If the initial symptom was tracheal compression and adequate surgery was performed, it is indeed a rare occasion for the surgeon to reoperate. Prophylaxis against a recurrence of compression symptoms in

neck. The involved glands with preservation of the muscular elements of the neck will preserve its anatomical appearance.[64]

5. It has been found that many low grade tumors of the thyroid (with malignant changes) may regress if a sufficient quantity of thyroid extract is given to suppress the thyroid stimulating hormone of the pituitary gland.

6. Thought must be given to the fact that a thyroid cancer may contain two or more elements of different tumor. These are similar to mixed tumors. This is especially true in patients under 35 years of age. The most commonly seen mixture in tumors of the thyroid is follicular carcinoma with papillary adenocarcinoma. The biological activity of these tumors approximates the papillary type although histologically, the appearance resembles the follicular carcinoma much more architecturally.

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6. Thyroid cancer is treated by surgery, radiation therapy, and/or radioactive iodine. In some cases all three methods may be employed.

7. Surgery is the *oldest and most commonly used therapeutic method*

14

Ectopic Thyroid and Other Anomalies

Being a highly vascular endocrine gland with powerful physiological activity, the thyroid may be the victim of embryological disturbances similar to other ductless glands of analogous potentialities

Ectopic thyroid tissue may be explained on the basis of one or both of the following[1-9]

1 Thyroid anlage may come to rest anywhere along the normal thyroid invagination during embryonic development This invaginating pathway extends from the tongue to the mediastinum Hence the presence of lingual thyroid thyroglossal cysts and intrathoracic goiters
2 Microscopic cellular thyroid anlages may be scattered or displaced to distant cell structures of similar physiologic destiny i e another endocrine gland Thus thyroid tissue may be found in an ovary or may be part of a teratoma wherever a teratoma may occur

Irrespective of its location thyroid tissue may undergo any physiopathologic change that is possible in a thyroid gland that is found in its normal anatomic location In other words the anomalous or ectopic thyroid may become a goiter in any of the varieties that normally placed thyroids give rise to [131] Moreover it is usually only when the ectopic or anomalous thyroid becomes pathologic that it is discovered It should be remembered that ectopic thyroid tissue may be the only thyroid in the patient and if it is removed myxedema may occur

The varieties of thyroid anomalies recorded are

1 Ectopic location of parenchyma
   a lingual goiters
   b Intrathoracic goiter
   c goiter plongeant
2 Teratomata
   a ovarian (struma ovarii)
3 Thyroglossal duct anomalies
   a cysts
   b sinuses

patients with struma lymphomatosa or Riedel s struma can be reasonably assured if the trachea is cleansed completely of thyroid tissue When it is not feasible to leave the trachea free of thyroid tissue then the next best procedure is to make certain that there is no contiguity of thyroid tissue between the thyroid remnants If the right remnant touches the left remnant, then there is a future possibility that there will be a bridge of tissue across the trachea which at some future time may be the nidus for recurrent thyroid growth and tracheal compression

Recurrence in thyroid cancer is a problem in itself Since cancer in the thyroid has various degrees of malignancy (depending upon its pathologic type and biological activity) it responds to therapy in a fashion corresponding to its type as described histologically and biologically The use of radical surgery radiation therapy and radioactive iodine have lowered the mortality and have given a more favorable prognosis to patients victimized by thyroid cancer

answered in this way It may be analogous to the te ticle and termed an unde cended thyroid[131] In this way too thyroids have been found at the ba e of the tongue between the foramen cecum and the hyoid bone They may project into the pharynx from the dor um of the tongue or actually be within or beneath the tongue A u eful point has been emphasized in reference to lingual goiter The point in question is that if no thyroid i th mus whatever can be palpated in the neck it is probable that the lingual

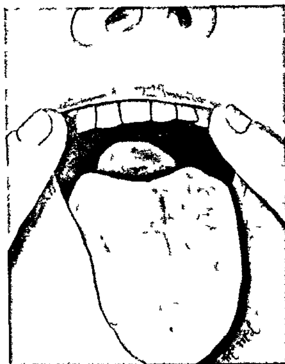


Fig 99 Lingual goiter (Means J H Thyroid and its Diseases Philadelphia J B Lippin ott 1937)

thyroid is an ectopic gland and not merely an accessory gland i e it is the patient s only thyroid ti ue[134]

When the thyroid descends too far and re ides within the thorax it is a true pathologic proce s and not an anomaly As the term intrathoracic or sub ternal implie it indicates that the lower pole or poles of the thyroid or a nodule of the gland has pa ed beyond the level of the upper border of the sternum More specifically the term ubsternal could be employed for those goiters with the greate t diameter above the ternum and intrathoracic for those in which it i below the sternum Means has sug

During normal embryonic development the thyroglossal tract from the foramen cecum to the pyramidal lobe of the normal thyroid usually dis

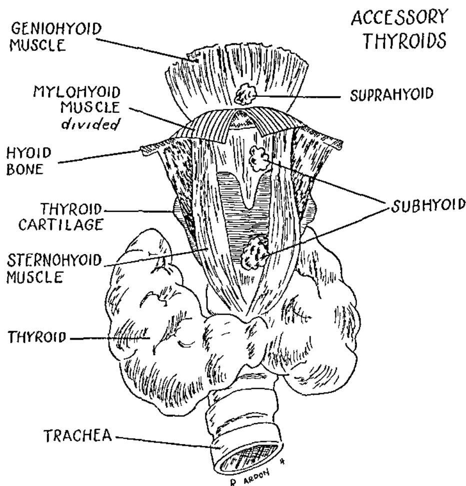


FIG 98 Sites where ectopic thyroid tissue may be found Tissue of this type is usually discovered in the cervical midline arising from misplaced anlage The term accessory thyroid has been used to identify this type of tissue The name aberrant thyroid tissue has been used also to indicate the same thing It is more accurate to employ the term accessory thyroid The above depicts two ectopic thyroid tissue sites represented in the suprathyroid and the subhyoid area

appears by midfetal life In its movements however it may leave behind small segments of tissue which may develop into accessory thyroids There may even be a complete failure of the entire thyroid structure to reach its normal destination in the pretracheal region *The lingual thyroid may be*

of years it grows quite large and heavy. The weight of the goiter becomes sufficiently ponderous enough to actually drop into the chest and come to rest on the diaphragm. This displacement may be less rapid in its course as when a goiter starts in the upper mediastinum and gradually finds its

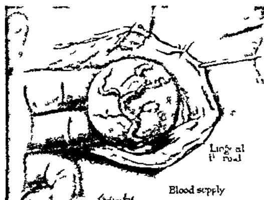


Fig 102 Further dissection enables the surgeon to elevate the tumor for removal after the tongue has been displaced into the operative site (Ward G E Cantrell J R and Allan W B Surgical treatment of lingual thyroid Ann Surg 139 May 1954)

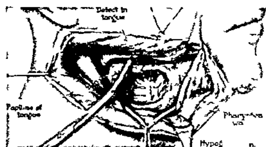


Fig 103 After the lingual thyroid has been removed a defect remains in the tongue The wound is closed and a temporary drain is usually employed (Ward G E Cantrell J R and Allan W B Surgical treatment of lingual thyroid Ann Surg 139 May 1954)

way into the lower thorax If the process is an insidious one and the transposition is gradual the examiner may speak of this as a migrating goiter

Teratomata are true embryologic anomalies In some teratomata (in lieu of the displacement of the thyroid anlage or a portion of it) there is a growth of thyroid tissue together with other tissues The ovaries are the commonest location for this symbiotic growth In a thyroid tumor of the ovary (struma ovarii) it appears as if the thyroid tissue has developed

gested the use of "incomplete intrathoracic" for the first and "complete intrathoracic" for the second[131] An intrathoracic goiter may be found years after the removal of a cervical thyroid Intrathoracic goiters are surgically important because they may produce mechanical pressure

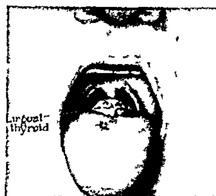


Fig 100 Lingual thyroid as seen through the mouth with the tongue pulled as far forward as possible (Ward G F Cantrell J R and Allan W B Surgical treatment of lingual thyroid Ann Surg 139 May 1954)

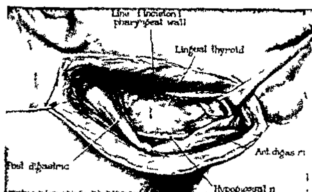


Fig 101 Surgical approach to lingual thyroid tumors This exposure of the lateral pharyngeal wall shows the tumor beneath the mucous membrane The pharyngeal incision is indicated by the dotted line (Ward G E Cantrell J R and Allan W B Surgical treatment of lingual thyroid Ann Surg 139 May 1954)

changes like other mediastinal tumors Lingual goiters on the other hand are surgical curiosities and removal is indicated because of inconvenience to the patient rather than for obstructive symptom

Goiter plongeant (diving goiter) is one that has plunged into the thorax and rests within that cavity in a dependent location[131] This type of goiter usually finds its origin in the neck or upper mediastinum Over a period

of the ovary That genuine thyroid ti ue is pre ent ha been demon d by chemical determinations of the iodine content a well a by bi lo al a ay [136] As a matter of record there are 4 ca e reported in which thyroid tumor of the ovary was actively functioning cau ing hy t oid signs and symptom [13 138] While thyroid tumors of the ov ry a u ually benign ca es have been reported in which malignancy w p ent with meta ta e and eventual death [13]



FIG 105 Surgical specimen of ovary demonstrating the gross appearance of struma ovarii The central black bulging gelatinous areas represent the thyroid elements (Courtesy A R Crane Ayer Clinical Laboratory of Pennsylvania Hospital Philadelphia)

Thyroglo al duct anomalies do not involve gland parenchyma Retention cysts due to a dragging down of pharyngeal tis ue during the growth of the thyroglo al tract are occasionally ob erved A cyst of this type may communicate with the pharynx at the foramen cecum via a fistulous remnant of the duct True external thyroglo al fistulae (tho e having an embryonic origin) do not occur ince the thyroglo al tract at no time communicates with the skin of the neck Pathologic external inu es may be formed by the external rupture of a thyroglo al cyst or when a surgical incision is made into it [131]

Thyroglo al cysts appear most often during infancy and childhood

at the expense of the other elements in the ovary.[135] While the histologic picture leaves little doubt as to the thyroid nature of the tumor tissue, one

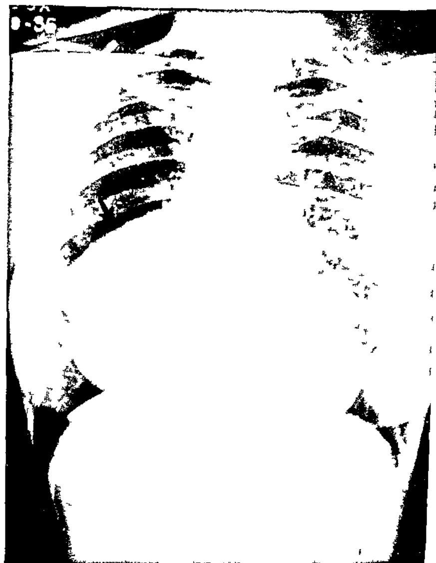


FIG 104 Goiter plongeant (diving goiter) The mass in the right chest (larger than the heart) is the goiter The right lower lobe of the lung reveals some atelectasis Goiter plongeant is a term applied to goiters which have plunged into the thorax (Means J H Thyroid and its Diseases Philadelphia J B Lippincott 1937)

may be misled by the pseudothyroid appearance At times this is seen as

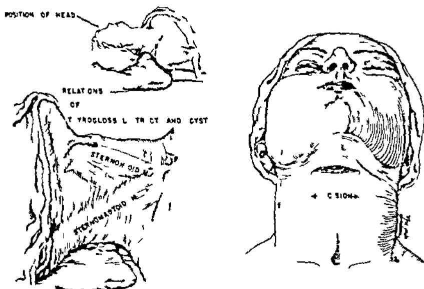


Fig 108 Illustrations of position of head and type of incision for removal of thyroglossal tract abnormalities in the upper neck. A similar type of incision is used for thyroglossal normalities in the lower part of the neck. (Redrawn from Si trunk.) (Ward G E, Hendrick J W and Chambers R G Thyroglossal tract abnormalities Surg Gynec & Obst 89 727 1949.)

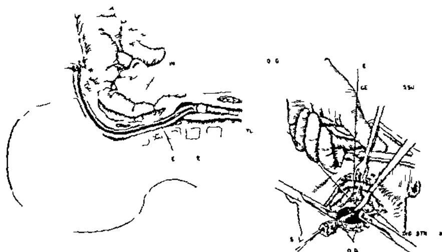


Fig 109 Endotracheal tube in place. Assistant's finger in the mouth forces base of tongue and foramen cecum forward facilitating coring out stalk of tract. (Modified and redrawn from Si trunk.) (Ward G E, Hendrick J W and Chambers R C Thyroglossal tract abnormalities Surg Gynec & Obst 89 727 1949.)



Fig 106 High power view of thyroid tumor of the ovary (struma ovarii) demonstrating thyroid tissue on the right and nonspecific ovarian tissue on the left (Picture No 88346 Courtesy of Armed Forces Institute of Pathology Washington D C)

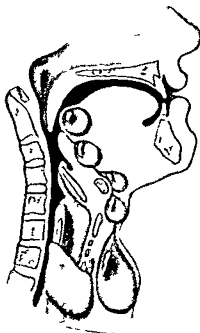


Fig 107 Sagittal view showing the locations of thyroglossal cysts (From Pfizer *Spectrum* appearing in the J A M A)

Infrequently they are seen initially during adult life They may become infected and drain pus via a fistulous opening at the foramen cecum or rupture externally As previously stated they may be incised surgically When any of these situations occur a draining sinus results Intermittent healing with reopening without permanent spontaneous healing is the usual trilogy of events In chronic cases the sinus tract may be palpated as a

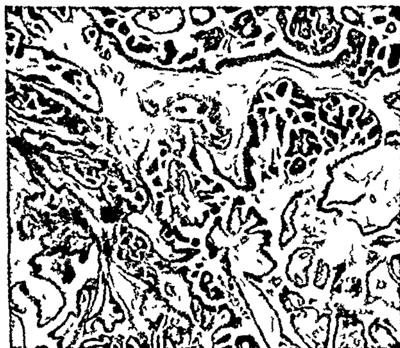


Fig 112 Histological section (× 40) of the operative specimen removed from the patient in figure 111 The cytoarchitecture is that of papillary adenocarcinoma as seen in some thyroid tumors (Byrne J J Carcinoma in a thyroglossal cyst Boston Med Quart [illegible] No 3 1960)

fibrous cord extending from the external opening to the level of the hyoid bone The sinus opening is usually found somewhere between the thyroid isthmus and the hyoid bone along the midline of the neck

Treatment of this condition consists of *a complete dissection and removal* of the entire sinus and cyst The tract must be followed as far as it goes in the direction of the foramen cecum It is usually necessary to remove a segment of the hyoid bone in order to insure a cure If any thyroglossal tract remains a recurrence is inevitable

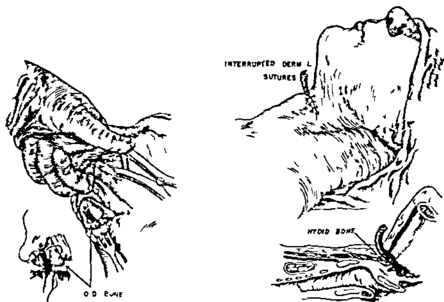


Fig 110 Method of suturing the hyoid bone and closing the wound Drain inserted (Redrawn from Sistrunk) (Ward G E Hendrick J W and Chambers R G Thyroglossal tract abnormalities Surg Gynec & Obst 89 727 1949)



Fig 111 Anterior and lateral views of a patient with a thyroglossal cyst in which carcinomatous change occurred (Byrne J J Carcinoma in a thyroglossal cyst Boston Med Quart 3 No 3 1950)

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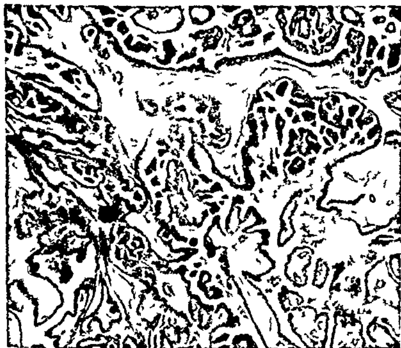


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Carcinoma in Chronic Thyroglossal Anomalies

The development of carcinomatous changes in a thyroglossal cyst or sinus is an unusual complication However this pathological change does occur and is often unsuspected until the pathologist's report is read When this complication is the result of a chronic sinus or cyst the microscopic picture of the neoplasm is quite similar to that seen in the thyroid gland itself The most common lesion is papillary adenocarcinoma Carcinoma in a thyroglossal anomaly should be treated similarly to carcinoma arising in the thyroid gland of similar histological appearance

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Exophthalmos

A MOST DISTRESSING complication of hyperthyroidism may be severe exophthalmos (also termed exophthalmia). This may be either unilateral or bilateral, stationary or progressive. Often it becomes so marked that specific measures are taken to prevent the loss of vision. Fortunately the use of modern methods for treatment has resulted in a lessening of the severity of exophthalmos.

Another good reason for the reduced incidence of exophthalmos is the exophthalmometer. Before its advent, surgeons used to label as exophthalmos any retraction of the eyelid or widening of the palpebral fissure (Dalrymple sign). Measuring with the exophthalmometer often indicates that exophthalmos is not yet present.

The following discussion on exophthalmos is adapted from an article by the late André Crotti, one of America's outstanding pioneers in thyroid surgery.[88]

Exophthalmos in Thyrotoxicosis

In the majority of instances there seems to be a direct relation between the severity of thyrotoxicosis and the degree of exophthalmos. The latter increases with the thyrotoxic syndrome or subsides with the disappearance of the toxic goiter. Hence the conclusion that exophthalmos is of thyroid origin. This point of view is corroborated by the fact that, as has been proved experimentally and clinically, forced feeding of desiccated thyroid can and does produce the thyrotoxic syndrome as well as the exophthalmos associated with thyrotoxicosis. It is further substantiated clinically by the results obtained with thyroidectomy.

However, in recent years the trend has been to regard the pituitary gland as the primary cause for thyrotoxicosis and its concomitant exophthalmos. The claim is made that an excess of thyrotropic hormone of the anterior pituitary in the blood acts as the primary initiator and induces hyperfunction, thus producing both the thyrotoxic syndrome and the exophthalmos.

There seems to be no question that there is an intimate functional relation between the thyroid and the pituitary in producing the thyrotoxic

syndrome What the intricate mechanism is no one knows The excess of thyrotropic hormone does not seem to be an adequate explanation however since there are diseases in which the thyrotropic hormone is present in abundance such as acromegaly or spontaneous myxedema where no thyrotoxic syndrome or exophthalmos appear

A frequent characteristic of thyrotoxic exophthalmos is the absence of mydriasis This sign is quite interesting Stimulation of the cervical sympathetic nerve produces exophthalmos with mydriasis This is to be expected since resection of the cervical sympathetic nerve will produce enophthalmos and miosis

In adenoma of the anterior pituitary acromegaly and the Cushing syndrome exophthalmos is observed long before the other clinical symptoms occur Here also mydriasis is absent This absence of mydriasis would make it appear that thyrotoxic exophthalmos and pituitary exophthalmos are the same

One should remember that exophthalmos experimentally produced with the thyrotropic hormone is by no means constant and that the effect upon the thyroid is fleeting and soon ceases to be active no matter how long it is administered On the other hand it would appear that thyrotropic hormone does not produce exophthalmos by activating the thyroid gland since exophthalmos is best obtained in thyroidectomized animals

Recently Dobyns and Wilson[350] reported that they had separated two substances in the pituitary secretion One of these substances is capable of producing hyperplasia in the thyroid gland The other can produce exophthalmos A few micrograms of the second substance can produce exophthalmos in the Atlantic minnow within 3 to 6 hours Some patients with severe exophthalmos have been studied and it was found that they have this substance in their blood sera

Another significant fact is that exophthalmos is observed only with thyrotoxic goiter and not with simple nontoxic goiter Furthermore postoperative progressive exophthalmos is observed only after thyroidectomy for thyrotoxic goiter and never after thyroidectomy for simple nontoxic goiter no matter how extensive the latter operation has been Now if thyroid insufficiency must be present to allow the thyrotropic hormone to produce exophthalmos why is exophthalmos not present in cases of postoperative myxedema following thyroidectomy for simple nontoxic goiter? That exophthalmos can be explained on the basis of disturbed autonomic control is perhaps probable but the role of the sympathetic system is not clearly understood It must be admitted that the intimate mechanism responsible for the production of exophthalmos is still unknown

However it is not difficult to understand the physical mechanism that induces eyes to bulge It is known that the retrobulbar tissues fat and

muscle undergo tropic disturbances and become edematous and that leukocytic infiltration takes place On the other hand the orbital space is a pyramid widely opened outside and sharply pointed inside The walls of the pyramid being completely bony are totally inelastic Pressure from within must of necessity push the orbital content forward and outward Thus it becomes obvious that if the orbital muscles become unduly hypertrophied and the orbital fat becomes so edematous as to occupy most of



Fig 113 Lateral view of a patient with severe exophthalmos and hyperthyroidism (Graham E A Surgical Diagnosis Vol II Philadelphia W B Saunders Co 1930)

the orbital space the globus oculi must necessarily protrude There is no other possibility

Otolaryngologic Causes of Exophthalmos

Disease spreading to orbital walls and contents from adjoining tissues may cause proptosis This of necessity must be differentiated from exophthalmos of thyroid origin Inflammation is most often responsible in children and young adults tumor in older people

Since the adoption of modern antibacterial drugs paranasal sinus infection rarely produces orbital cellulitis Ethmoid cells are the most frequent source in babies and small children since the eye socket is protected

only by the very thin lamina papyracea In young adults particularly the beetle browed the orbit is generally infected through the frontal sinus O teitis occurs then edema of the socket with pain and fever The lids are dusky red soft and swollen If pus form in the orbit proper the globe is moved forward and outward or downward

Acute ethmoiditis seldom produce orbital ab ce s or cellulitis re quiring drainage But if cellulitis re ults from acute frontal sinu iti trephination should be done through the sinu floor without delay

As a general rule tumors causing exophthalmos are benign when origi nating in the frontal sinus and malignant if ri ing in the maxillary or ethmoid Mo t frontal growths are mucoceles which grow slowly and rarely cau e *inflammation Occasionally o teomas are seen* Both type should be removed completely by an external frontoethmoid procedure

Sarcoma and carcinoma occur with about equal frequency the former at any age the latter chiefly at 40 year and older Carcinoma of maxillary origin i more common than ethmoid and rarely frontal carcinoma i en countered Na opharyngeal tumors seldom reach as far as the orbit

Antral neopla ms cause pain in the upper teeth and cheek buccal swelling ane thesia of skin and upward di placement of the eye Ethmoid growths soon break into na al and orbital cavities producing epiphora diplopia exophthalmos with palpable tumor foul bloody di charge and severe pain Wide surgical removal may be effective unless the deep cervical lymph glands are involved If metasta is has occurred only palliative radiation is of use

Tumors in Children During infancy and childhood the primary orbital tumors are hemangioma optic nerve glioma dermoid teratoma and me enchymal tissue tumors

Hemangiomas often extend far enough forward to cau e vi ible dis coloration Growths in young people are usually radio en itive

Gliomas of the optic nerve though histologically benign may cau e *optic atrophy and blindne or invade the brain and di tort the pituitary* fossa Tumors are exci ed intracranially unroofing the optic canal and orbit if nece ary The eye is then removed anteriorly

Congenital tumor including dermoid and teratoma ari e out ide the muscle cone and may cau e lateral or vertical di *placement of the globe* Dermoids often grow at suture lines and penetrate the skull Roentgeno grams are made to show bony dehi cence A neurosurgeon should collabo rate with the ophthalmologist in the surgical treatment

Undifferentiated sarcomas of the orbit are among the mo t malignant neoplasms of childhood the least dangerous being rhabdomyosarcoma Immediate exenteration i ordinarily advi able preceded or followed by irradiation

Tumors in Adults A common tumor of adults is hemangioma The diag

nosis may be confused by calcification and hyperostosis. Growths are usually nonmalignant in nature and radio-sensitive.

Meningioma originating near or in the orbit quickly produces papilledema and optic atrophy, often hampers eye movement and generally causes hyperostosis. It is not found often in individuals under 30 years of age. True bony tumors are seen before the age of 20 in most instances.

So-called "mixed" tumors of the lacrimal gland displace the eye downward and nasally and frequently decrease the flow of tears. They recur locally and destroy bone. Roentgen therapy is usually ineffectual.

Retrobulbar lymphomas are of all types ranging from benign to malignant and all are quite susceptible to radiation. The origin is ill defined and prognosis is uncertain.

Tumors of Schwann's sheath such as neurofibroma, neurinoma, neuroma and melanoma may begin initially in the orbit.

Also, a great variety of lesions may encroach from neighboring tissues or metastasize from afar. In every unexplained case of exophthalmos, diligent search is most essential.

Abnormal arteriovenous shunts from injury or other factors may cause pulsating protrusion of the eye with audible bruit and palpable thrill. Vertical extraocular muscles are usually paralyzed since lesions are often in the carotid sinus wall. In some instances craniotomy can be done and involved vessels ligated.

Either or both eyes may be thrust forward by systemic disorders including angioneurotic edema, infection and xanthomatosis such as Schuller-Christian disease.

Progressive Postoperative Exophthalmos

This condition, although not common, has been and still is the most baffling problem confronting the physician and surgeon. It is frequently the only remnant of the disease that once existed. Its characteristic is to be progressive, leading sometimes to almost complete extrusion of the eyeballs, total blindness and panophthalmitis with all its consequences.

Progressive exophthalmos is more common in men than in women. In this connection it is interesting to recall that Marine observed male rabbits to be more susceptible than female rabbits to the experimental production of exophthalmos.

The majority of thyrotoxic patients with exophthalmos recover fully after thyroidectomy. The thyrotoxic syndrome disappears altogether or almost completely. Exophthalmos, however, when present, subsides more slowly. Sometimes it remains permanently stationary with no untoward effect on the patient[88].

In a few instances, sometimes months or even years after thyroidectomy

exophthalmos reappears and follows a progressive course until the lids can no longer cover the bulbus The lids become extremely puffy and the ocular movements more and more restricted The conjunctiva becomes congested and swollen to such an extent that it herniates through the lids Lacrimation becomes very annoying Being unprotected the cornea becomes inflamed, finally ulcerates and panophthalmitis follows In the meantime the eye sight has been totally lost The only course open is enucleation otherwise death will ensue Ordinarily the patient has a low metabolic rate in the presence of these severe eye findings

The theory that thyrotoxic exophthalmos and progressive postoperative exophthalmos are produced by the same mechanism seems justified To be sure there are differences In thyrotoxic exophthalmos the mobility of the eyeball is not impaired or at least very slightly impaired In progressive postoperative exophthalmos the impairment is marked The upward and downward rotation ceases first later the inward and outward motions disappear In thyrotoxic proptosis there is usually no chemosis In the postoperative progressive exophthalmos, hyperthyroidism is usually the rule In thyrotoxic exophthalmos the reverse is usually true namely hyperthyroidism is absent in the presence of the eye pathology

In both forms of exophthalmos mydriasis is absent In the two forms also the trophic orbital disturbances are the same Changes in the retina occur in both forms of exophthalmos but only in the last stages of the disease

In the last analysis however these two forms of exophthalmos must have a common origin The trophic disturbances of the orbital muscles are probably primarily caused by stimulation of the sympathetic nerve, which in turn brings about trophic disturbances Biological and chemical reactions must also play a part in the production of the syndrome

One thing remains to be explained Why is it that, even after all other thyrotoxic symptoms have subsided exophthalmos still persists for a long time and sometimes permanently? Probably this happens because the eyeball having protruded for so long a time has lost the "right of domicile in the orbit It has acquired new relations connective tissue and retrobulbar fat have filled the dead space left by the eyeball while it protruded and it is difficult or even impossible for the globus oculi ever to return to its normal position

Why is it that thyrotoxic thyroids do not all produce exophthalmos? We do not know After seeing a large series of thyrotoxic goiters one notices that in certain thyrotoxic patients the toxic effects of the hyperthyroid gland seems to center their deleterious effects upon certain organs or systems of organs In some patients the cardiovascular system seems to be affected disproportionately to the other organs In other patients it is the

gastrointestinal system that is heavily attacked by thyrotoxicosis with vomiting and diarrhea as cardinal complaints In still other patients the ocular system is most markedly involved This would lead one to believe that certain organs or systems of organs may be unduly sensitized to thyroxin while other are resistant to it On the other hand the concept of sensitization as an activator may well have an opposite effect, namely to act as an inhibitor as for instance with the production of a low metabolism

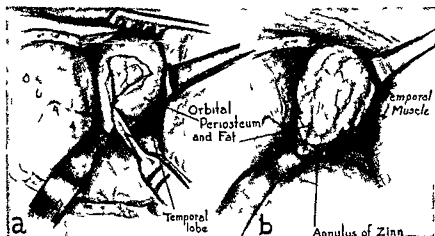


Fig 114 Diagrammatic illustration of the various steps in the operation for intractable exophthalmos *A* Through a parietal flap with the frontal lobe elevated the bones of the orbital roof have been removed with a rongeur The orbital periosteum has been incised and the underlying fat is brought into the incised area *B* There is an upward bulging of the retrobulbar fat and the retro ocular muscles with a resulting diminution of the forward pressure on the eye (Lahey F H Surgery of the thyroid gland New England J Med **236** 46-62 1947)

Treatment of Exophthalmos

One must treat the thyrotoxicosis first The earlier this condition is treated and cured the greater the chances that exophthalmos will subside and disappear One should always remember that whenever ocular signs appear early in cases of thyrotoxic goiter these signs and the conditions that cause them if allowed to go unchecked will quickly become severe

The Exophthalmometer In the early stages of thyrotoxicosis exophthalmos is frequently diagnosed when in reality it is not present at least not yet The presence of the Dalrymple sign namely retraction upward and downward of the eyelids is responsible for the mistaken diagnosis

Measurements with the exophthalmometer will soon determine whether exophthalmos is present or not. Measurements in excess of 18 must be regarded as abnormal, especially if there is a difference in the measurements of the two eyes.

Since patients with progressive exophthalmos are, in the majority of instances, hypothyroid, thyroid extract is given. To this iodine is added,

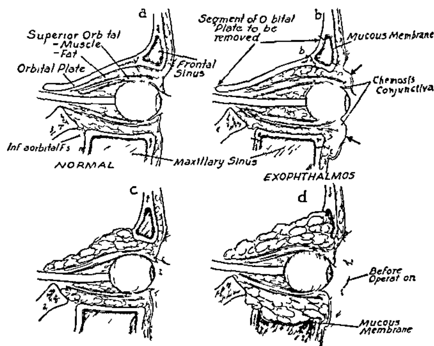


Fig 115 Diagrams of the various steps in the operation for supraorbital decompression of the eyeball for intractable exophthalmia. These are lateral views showing how the operation results in an increase in the space confining the eyeball. With such increase there is a regression of the exophthalmia. (Lahey, F. H. Surgery of the thyroid gland. New England J. Med. 236: 46–62, 1947.)

the idea being that it will be helpful if thyrotoxic signs are present and, if not, will act as a deterrent to the edema of the tissues.

Cervical Sympathectomy. Cervical sympathectomy, as it was performed, has been abandoned. The new antithyroid drugs have proved disappointing in alleviating exophthalmia except when hyperthyroid symptoms are present.

Electrocauterization of the hypophysis and its stalk. This procedure carries with it the danger of pituitary deficiency manifested by general weakness, a very low basal metabolic rate, sexual impotence, testicular

atrophy and hypoglycemia (McCullagh) However some good results have been obtained



Fig 116 *A* Patient with severe exophthalmos This photograph was taken several weeks prior to supraorbital decompression procedure (All photographs in this series are through the courtesy of Howard C Naffziger Department of Neurological Surgery University of California Medical Center)

B Same patient showing marked proptosis one week prior to surgery

C Lateral photograph of the same patient taken the day before operation

D Anterior view taken the day before operation showing the rapid advancement of exophthalmos in one week Note the rim of edema above lower eyelids

Irradiation of the Pituitary This therapy has been found useful in a few cases but has given totally negative results in others

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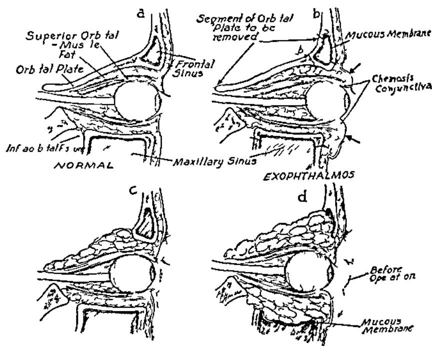


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drug was given. Recurrence of the signs and symptoms were noted when the drug was stopped. Therefore treatment must be given for a long period of time.[61]

There appeared a study in the *Journal of Endocrinology* concerning the treatment of malignant edematous exophthalmos via surgical hypophysectomy. This procedure was performed after intensive treatment with all types of medical therapies. Following surgery there was a remarkable improvement in the exophthalmos. Histological examination of the tissue removed at surgery showed an increase in the numbers and in the secretory activity of cells that are considered to be the site of production of the thyroid stimulating hormone. It is of value to know that in some patients in whom hypophysectomy has been performed for malignant disease clinical hypothyroidism developed within 4 to 8 weeks following operation. The thyroid gland itself has been found to have an increase in fibrosis and in other glands a slight increase in the height of the follicular epithelium cells was noted.[633]

Orbital Decompression of Naffziger Orbital decompression consists of removing the superior orbital plate and unroofing and removing the bone covering the optic foramen This will permit the orbital content to move upward and in consequence, will do away with the intraorbital forward push on the eyeball It is mandatory to unroof the optic foramen so as to release pressure on the optic nerve A pressure bandage over the tightly closed eyelids is necessary in order to push the eye backward Orbital decompression should be done, especially when the optic nerves show signs of being destroyed or embarrassed

Although this operation devised by Naffziger will not always abolish the unsightly exophthalmos it will, if done in time, prevent ulceration in





E Photograph taken immediately following operation (Supraorbital decompression procedure performed by Howard C Naffziger University of California Hospital)
F Postoperative photograph of the same patient looking to the right

fection and, if loss of blood supply has not already taken place save the eye It will obviously be of no value however to patients who are sent for operation when the eyeball is practically falling out of the orbital socket

Recently several French investigators have used cortisone and corticotropin in the treatment of 15 patients with hyperthyroid edematous exophthalmos In the cases studied the degree of exophthalmos was not directly proportionate to the severity of the hyperthyroidism In fact some of the patients with the severest exopthalmia had hypothyroidism The use of the steroids showed an improvement in the edematous exophthalmos in a matter of hours The improvement manifested itself on the edema chemosis and the subjective symptoms particularly Ocular protrusion was not reduced remarkably The best results were obtained when the drug was administered early in the disease The improvement continued as long as the

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Hyperparathyroidism

No discussion on disorders of the thyroid gland would be complete without some remarks on the parathyroid and its disorder. Most physicians and surgeons rarely consider hyperparathyroidism when they are studying a patient. For this reason the diagnosis may not be arrived at until the patient has harbored the disease for months or years.

Laboratory and Clinical Picture

Although there have been many excellent reviews on hyperparathyroidism, the diagnosis unfortunately is not often accurately made. This may be due perhaps to the widespread misbelief that diseases of the bone are a requisite in the clinical picture of hyperparathyroidism. It may also be due to the fact that some internists and surgeons believe that the diagnosis cannot be substantiated if only minimal hypercalcemia is present. It is well to remember that the presence of renal calculi is an indication that excessive parathyroid activity must be eliminated. In addition it is well to emphasize that hyperparathyroidism may at times produce only a minimal elevation of serum calcium. The power of the kidneys to excrete an increased amount of calcium may be severely taxed during the process of calcium excretion.

The excessive amount of calcium in the urine may be detected by the Sulkowitch test. This is a qualitative analysis of the urine. Although this test may also be found positive in other conditions, it is nevertheless an available diagnostic aid in evaluating patients with hyperparathyroidism. The Sulkowitch reagent is a solution containing 2.5 Gm. of oxalic acid, 2.5 Gm. of ammonium oxalate, 5 cc. of glacial acetic acid, and water to a final volume of 150 cc. When this solution is mixed with urine containing calcium, a fine white precipitate of calcium oxalate appears within a few seconds. By mixing this reagent and urine one can differentiate between urine with no calcium (no precipitate), urine with a normal amount of calcium (moderate precipitate), and urine with an excessive amount of calcium (heavy precipitate).

The measurement of renal reabsorption of phosphorus appears to be a valuable diagnostic test for primary hyperparathyroidism, even in patients

with moderate renal impairment Schaaf and Kyle [9] reported that in healthy subjects, renal pho phorus reab orption is about 91 per cent, whereas patients with primary hyperthyroidi m have only about 58 per cent reab orption Their method utilizes blood and urine determinations of pho phorus in conjunction with endogenous creatinine clearance estimate of glomerular filtration rate The ratio of reab orbed to filtered pho pho ru , *multiplied by 100, is an estimate of the per cent of renal phosphorus* reab orption

On occasion it may be nece ary to employ the Bauer Aub diet as an other valuable means of arriving at exce ive parathyroid function This *diet contains approximately 135 to 150 mg of calcium per day* The diet is a neutral ash low calcium diet con isting of vegetable fruit meat cereals and oleomargarine Butter milk chee e cream and cereals forti fied with calcium are prohibited The patient is fed this diet for one week during this time the patient is not kept at bed re t At the end of the week a 24 hour urine specimen is collected and the calcium content is quanti tatively analyzed The exact content of the diet is pre ented in Albright and Reifenstein s textbook [1]

A new test of parathyroid function involves the study of pho phaturia induced by calcium infu ion French authors reported the effects on phos phaturia of an infusion of 3 3 Gm of calcium chloride in 500 cc of i otonic glucose solution A diure is greater than 500 cc in 3 hours was noted in control subjects, together with a decrea ing hourly pho phaturia This lead to a 24 hour phosphaturia that was definitely lower than that before and during the first 24 hours after infu ion though the latter is often higher than the initial pho phaturia In the patient with po toperative or idio pathic hypopar athyroidi m who had not received tre atment there was a decrea ed diuretic re pon e and a frank hyperpho phaturic re pon e both in the hourly and 24 hour pecimens There was no abnormal elevation of pho phaturia in the 24 hours after infusion In patients with hypopara thyroidism who were treated these re pon es were attenuated or even re ver ed In spa mophilia (idiopathic normocalcemic tetany) and in the so called endocrine cataracts there was no definite di turbance of the diuretic re pon e and the 24 hours pho phaturia On the other hand the hourly hy popho phaturia re ponse was modified It was e tabli hed lowly and pro gre ively in pasmophilia and was retarded in the cataracts after a pha e of complete absence during which there was transient hyperphosphaturia [4]

The foregoing study on pho phaturia is another adjunct in the laboratory diagnosis of parathyroid di turbance Although this is only a preliminary report neverthele s it may be employed in tho e borderline ca es when every available diagno tic aid is needed in the evaluation of a patient s clinical picture The value of this te t is enhanced when one realizes that

it is fairly well established that the muscular symptoms presented by the patient are due to hypophosphatemia

Primary hyperparathyroidism is usually the result of a solitary benign adenoma of one of the parathyroid glands Rarely is this hyperfunction the result of all the parathyroid glands Multiple adenomata and malignancy of the parathyroids is likewise not a common occurrence

The clinical picture resulting from adenoma of the parathyroid is due to



Fig 117 Gross specimen of a parathyroid adenoma (Attie J N and Perlmutter M Diagnosis and treatment of hyperparathyroidism New York State J Med 52 No 19 1954)

excessive secretion of the parathyroid hormone The exact site of its action is controversial However for purposes of discussion it will be assumed that the primary function is to control the excretion of the phosphate ion by the renal tubule In the presence of excessive hormone phosphate excretion is increased and the level of phosphate ion in the blood diminishes As a result of the disturbance in the ratio between the calcium and phosphorus ion in the blood both ions are withdrawn from the bone and a stimulus is provided for increased osteoblastic activity with its accompanying rise in the alkaline phosphatase of the blood In this manner the chemically diagnostic features are produced namely high blood calcium low blood phosphorus and increased alkaline phosphatase The elevation in the quantity

of calcium ion in the blood necessarily leads to an increased excretion of calcium in the urine

The symptom complex therefore falls into three categories

1 The result of high blood calcium
2 Excessive urinary calcium and phosphorus
3 Secondary bone changes

When symptoms result from an elevated blood calcium the diagnosis is



FIG 118 Photomicrograph (1 0 ×) of a parathyroid adenoma The cytoarchitecture is that of parathyroid tissue composed of compact columns of opaque epithelium arranged in a palisade form Much variation in the size and appearance of these columns is noted Many areas are quite vascular where the cell columns are small

difficult without laboratory studies because the symptoms simulate many functional disorders These symptoms are

Muscle weakness
Fatigue
Anorexia
Nausea
Vomiting
Constipation
Lethargy
Bradycardia
Cardiac Irregularities

The hypercalcemuria and hyperphosphaturia in the early stages, may be

manifested merely by polyuria and polydipsia, which may be misinterpreted as diabetes insipidus Later renal calculi develop and symptoms



Fig 119 X ray film of the right humerus demonstrating cystic bone disease in a 25 year old female with hyperparathyroidism

appear from renal colic, or superimposed renal infection, and still later renal insufficiency The secondary effect on the bony structures leads to a variety of disorders These may be one of the following

Cysts



FIG 120 Roentgenogram of right femur showing osteitis fibrosa cystica (proven by biopsy) in a 50 year old housewife with hyperparathyroidism

Fractures
Tumors
Deformities
Absence of lamina dura

manifested merely by polyuria and polydipsia, which may be misinterpreted as diabetes insipidus. Later renal calculi develop and symptoms



FIG 119 X ray film of the right humerus demonstrating cystic bone disease in a 25 year old female with hyperparathyroidism

appear from renal colic or superimposed renal infection, and still later renal insufficiency. The secondary effect on the bony structures leads to a variety of disorders. These may be one of the following

Cysts

fact that in the former more parathyroid hormone is produced than is necessary whereas in the latter the increased production of the hormone aims



Fig 1[illegible] Nephrocalcinosis in a patient with hyperparathyroidism (Attie J N and Perlmutter M Diagnosis and treatment of hyperparathyroidism New York St J Med 52 1954)

at compensating calcium losses Secondary hyperparathyroidism is therefore a physiological process that serves to protect the organism from a

Relationships Between Parathyroids and Bone Diseases

The mechanism of bone formation is not entirely understood but probably the parathyroid influences the process by maintaining an adequate concentration of calcium and phosphorus in the blood A functional insufficiency of these glands leads to uncontrolled osteogenesis with calcification of the cartilages and ligaments in addition to increased density of the bones

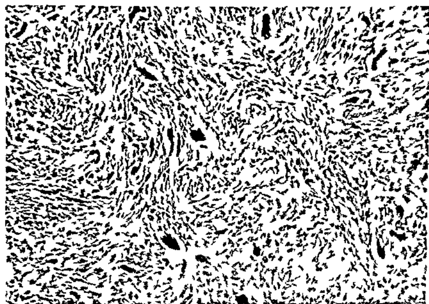


Fig 121 Photomicrograph (150 ×) showing osteitis fibrosa cystica This specimen was obtained via biopsy from the patient in figure 120 The characteristic feature of the lesion are minute smooth walled cysts lined by cellular tissue and large giant cell tumor tissue

already formed A normal functioning of these glands insures the best bone formation The calcium regulating action of these glands is demonstrated by the fact that if the blood calcium diminishes for causes other than a condition of the parathyroids these draw calcium from the bone to protect the organism against the dangerous consequences of hypocalcemia When calcium decreases and tetany appears the parathyroids become hyperactive (secondary hyperparathyroidism) and eventually become hyperplastic It is therefore always necessary first to determine whether a case of hypocalcemia is the result of idiopathic hypoparathyroidism in which case there would be no functional reaction of these glands The difference between primary and secondary hyperparathyroidism lies in the

3 Lassitude
4 Muscle weakness
5 Cardiac arrhythmia and occasional slow pulse

B *Transportation and excretion of calcium*
1 Renal complications (lithiasis)
2 Polyuria and polydipsia
3 Enuresis nocturia and dysuria

C *Skeletal system*
1 Pain in joints and bones
2 Spontaneous fracture
3 Cysts in long bones and skull
4 Deformity of long bones
5 Kyphosis scoliosis or deformity of the thorax
6 Waddling gait and inability to walk

Secondary Hyperparathyroidism

The pathologic characteristic of secondary hyperparathyroidism is hyperplasia of all the parathyroid tissue in contrast to the neoplastic involvement usually of one gland in the primary type. This hyperplasia is considered to be a compensatory response to metabolic disturbances resulting from renal or osseous disease. Infrequent causes are metastatic carcinoma of the bone, multiple myeloma, osteomalacia and rickets; however, the most common cause is chronic renal disease. The essential feature appears to be a lesion, congenital or acquired, which leads to chronic renal failure of such an insidious nature that it is compatible with survival over a long period of time. While the presenting picture may be related primarily to the renal insufficiency, it is a peculiar characteristic, especially in young individuals, that the renal dysfunction may be so obscure that the individual is considered to be relatively healthy.

It is interesting to note that the Mayo Clinic reported 2 cases of intrathyroid hyperfunctioning parathyroid adenomata which were removed by incising the thyroid gland. A photograph of the microscopic sections appears in this chapter.

Familial Hyperparathyroidism

An interesting case report by Frohner and Wolgamot reviewed 5 cases of hyperparathyroidism in one family.

Case report. Evidence obtained from the study of 5 siblings, each of whom was found at operation to have one or more parathyroid adenomas, supports the belief that primary hyperparathyroidism may be a familial disease. Rickets (osteomalacia), pregnancy, calcium deficiency, and renal insufficiency, all of which are known to produce diffuse hyperplasia of the parathyroid gland, could not be considered as primary factors in the condition found in these patients. Their consumption of milk was average

hypocalcemia induced by causes other than parathyroid insufficiency But it does at the same time impair the bones If the hypocalcemia lasts long the bones undergo a marked loss of calcium because of the action of the parathyroid especially *in cases in which calcium absorption is deficient* Diseases in which secondary hyperparathyroidism may determine bone lesions are rickets osteitis fibrosa cystica (Recklinghausen's disease) chronic renal insufficiency, and Fanconi's syndrome In addition calcification of blood vessels or deposition of calcium in muscle tissue may be visualized by x ray

In 1954 Walton[16] presented histories of two premature infants who *presented signs of tetany such as twitching and tremors with and without* convulsions Antitetanic treatment consisted of the administration of calcium chloride and aluminum hydroxide gel in the formula and 10 per cent calcium gluconate intravenously The occurrence of tetany in these two siblings led to the discovery of primary hyperparathyroidism in the mother Surgical exploration of her neck was carried out and a parathyroid adenoma was removed from the inferior pole of the left lobe of the thyroid gland *These cases demonstrate the important role that prenatal* factors may play in influencing the parathyroid state of newborn infant The mechanism of intrauterine suppression of fetal parathyroid gland is incompletely understood It is obvious that maternal primary hyperparathyroidism can exert transplacental influence and it seems likely that secondary hyperparathyroidism of pregnancy can also exert a transplacental influence Since the former has an associated high serum calcium and the latter a low serum calcium the author suggests that the transplacental suppression is mediated not by calcium or phosphate ions but by parathyroid hormone The author feels that the occurrence of tetany in premature or breast fed infants or in a severe form in any infant should *lead one to suspect hyperparathyroidism in the mother Review of the liter*ature reveals an apparently increased incidence of stillbirths miscarriages and premature births in mothers with primary hyperparathyroidism

The onset of hyperparathyroidism produces bizarre and ill defined symptoms which may easily be overlooked unless blood calcium studies are done Norris concluded in his review that the average duration of symptoms before surgery has been from 5 to 7 years while Albright Aub and Bauer[1] *reported* a case in which they believe the adenoma had existed for 39 years [13]

Shelling and Keyser adequately classified the symptoms [13] They are presented here as a summary of the clinical picture of hyperparathyroidism

A *Hypercalcemia*

1 Hypotonia

2 Chronic constipation

3 Lassitude
4 Muscle weakness
5 Cardiac arrhythmia and occasional slow pulse

B *Transportation and excretion of calcium*
1 Renal complications (lithiasis)
2 Polyuria and polydipsia
3 Frequency, nocturia and dysuria

C *Skeletal system*
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2 Spontaneous fracture
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and they had all received cod liver oil regularly in childhood Only one had any impairment of renal function though all had renal disease (nephrocalcinosis in 3 a

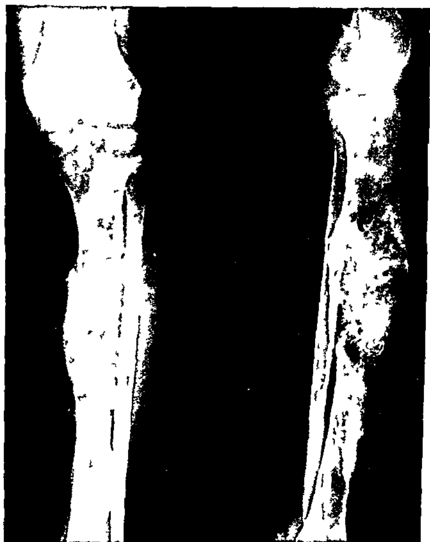


FIG 123 Osteogenic sarcoma of the tibia arising in Paget's disease of the bone This lesion is rarely associated with secondary hyperparathyroidism It is of value to know that approximately 8 per cent of patients with Paget's bone disease develop sarcoma

staghorn calculus in 1 and hematuria and renal colic due to stone in the last) The possibility of excess phosphate ingestion cannot be ruled out at present the soil of the patients home locality, however does not differ significantly from Montana soil in general Studies of the drinking water which comes from a creek are now under way

he did not have diabetes Hyperparathyroidism cannot be proved in his case but during the last 15 years of his life he suffered from kyphosis polyuria nocturia and weakness—all classic symptoms of parathyroid disturbance The patient's mother is in good health but she has a suspiciously low serum phosphorus level A low serum phosphorus level was also found in an otherwise normal sibling of the patient. Study of the rest of the family consisting of another sibling and 7 children of the patients showed that all were normal Investigation of the patients for a tumors of the pituitary gland and pancreatic islet cell tumors and duodenal ulcer—two sets of ab-



Fig 124 Photomicrograph (150 ×) showing Paget's bone disease Fibrosis and irregular trabeculations composed of intercalated segments of bone with a mosaic like appearance are seen This histologic picture is compatible with repeated destruction and formation of new bone In this case the serum phosphatase was 13 9 units calcium 12 8 mg and phosphorous 4 0 mg For a differential diagnosis compare this picture with that demonstrating osteitis fibrosa cystica (figure 121)

normalities that have been described as occurring with hyperparathyroidism—proved negative

Diagnosis

By means of the clinical picture and laboratory studies discussed at the beginning of this chapter one may make the diagnosis of excessive parathyroid activity Succinctly it can be stated that diabetes insipidus may on occasion resemble hyperparathyroidism For this reason this type of diabetes must be considered in the differential diagnosis

During the past year Curtiss and his associates[38] have observed 4 mal patients in whom severe compression fractures of the vertebrae develope during the administration of cortisone or corticotropin, or both Althoug demineralization of the skeleton is a recognized complication of cortison therapy, these cases have emphasized the importance of possible patho logical fractures when prolonged treatment of this type is employed Unde these circumstances especially if a patient develops a pathological frac ture attention may be called to the parathyroid gland Thus it is well t

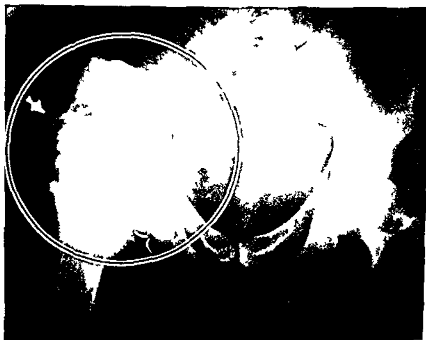


Fig 125 Pathologic fracture of the hip due to sarcoma of the bone Bone lesions of this type may be associated with secondary hyperparathyroidism

bear in mind that excessive cortisone therapy may result in bone lesions which may erroneously be attributed to hyperparathyroidism

As to the laboratory studies as an aid in diagnosis the trinity which leads one to suspect hyperparathyroidism is high blood calcium low blood phosphorus and an elevated alkaline phosphatase

Diagnostic Sign in Hyperparathyroidism

At the Stanford University School of Medicine Fender[148] has described a sign which he has noted in hyperparathyroidism He has described this as a "watermelon sound" resulting from percussion of the patient's head

"Instead of the high pitched crack as evoked from a normal adult skull there emerged a booming low pitched note that reminded me of the sound



Fig 126 X ray film showing lymphosarcoma of the humerus (proven by biopsy) This lesion is not usually associated with secondary hyperparathyroidism

made by tapping on a watermelon It turned out that the patient had hyperparathyroidism

Tape recordings were made by placing a crystal type of Electrovoice microphone 1 cm from the scalp A Magnacorder type PT6AH was used

During the past year Curtiss and his associates[38] have observed 4 male patients in whom severe compression fractures of the vertebrae developed during the administration of cortisone or corticotropin or both Although demineralization of the skeleton is a recognized complication of cortisone therapy the cases have emphasized the importance of possible pathological fractures when prolonged treatment of this type is employed Under these circumstances especially if a patient develops a pathological fracture attention may be called to the parathyroid gland Thus it is well to

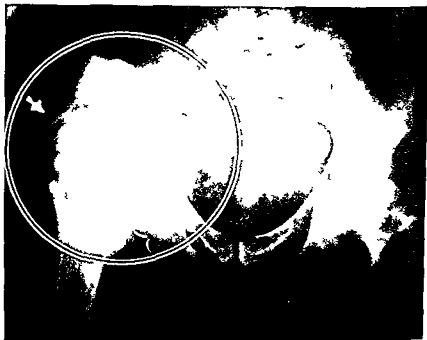


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The resulting sound was recorded in addition to an x ray photograph of the patient in question The report of the radiologist indicates that "the appearance of the skull is strongly suggestive of hyperparathyroidism"[148] This diagnostic sign is offered for the reader's own evaluation



Fig 129 Roentgenogram of the skull of a patient with hyperparathyroidism Note the fuzzy appearance of the diploic bones (Fender F A Diagnostic sign in hyperparathyroidism J A M A 154 March 17 1954)

Treatment

The treatment of hyperparathyroidism is surgical When a diagnosis of excessive parathyroid activity has been indicated as the etiological agent for the clinical symptoms presented in a patient exploration of the neck is imperative *In all probability an adenoma may be the cause for the symptom complex* Removal of the parathyroid tumor results in an amelioration of the symptoms



Fig 127 Microscopic section of a parathyroid adenoma found within the thyroid gland The adenoma is seen lying in immediate apposition to thyroid tissue (hematoxylin and eosin stain 50 ×) It is noted that there is an absence of any intervening fibrous tissue septum which might represent a capsule The tumor was found when the right lobe of the thyroid was divided in a longitudinal plane (Black B M and Haynes A I Intrathyroid parathyroid adenomas Proc Staff Meet Mayo Clin 24 No 16 1949)

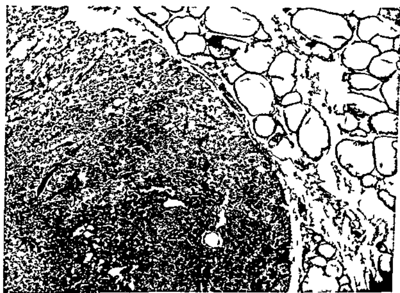


Fig 128 High power microscopic view of adenoma described in figure 127

	C d y	B dl
Length	6 mm	3 to 15 mm
Width	3 mm	to 4 mm
Thickness	2 mm	2 to 4 mm

Fortunately when an adenoma is present it is much larger than a normal parathyroid Thus its identity is more readily revealed Even though a parathyroid adenoma is larger than a normal parathyroid gland it is often most difficult to locate this lesion If the surgeon will recall that most parathyroid tumors are in locations near the thyroid vessel he will be rewarded on many occasions by finding the adenoma If the surgeon follows the blood vessels especially the inferior thyroid artery he may find an adenoma migrating in the direction of the mediastinum or subclavicular area The presence of an adenoma in the mediastinum is not unusual and should be considered at the operating table

Catlow reported a case which well illustrates this situation [1,6] In a 50 year old man whose case is reported the history and the blood calcium values indicated hyperparathyroidism Surgical exploration of the neck disclosed no parathyroid adenoma It was decided that at a second operation the superior mediastinum should be explored This was done However on the 4th postoperative day bilateral pneumonia developed it was followed by cardiac decompensation and death on the 5th postoperative day Autopsy revealed a mass in the superior mediastinum which on microscopic study showed the typical picture of a parathyroid adenoma This case emphasizes the necessity of exploring the mediastinum after fruitless neck exploration for parathyroid adenoma

In view of the report from the Mayo Clinic it is apparent that a parathyroid adenoma may be found in the substance of the thyroid gland itself With this knowledge as a basis it would seem logical to incise the thyroid gland itself when an accurate diagnosis of hyperparathyroidism has been made and surgical exploration in the usual manner has failed to reveal the pathology sought Under these circumstances it would be well for the surgeon to incise the thyroid across the isthmus divide it completely in half and expose both lobes laterally When this has been accomplished a parathyroid adenoma may be found in the inferior borders of either the right of left thyroid lobe

Effects of Parathyroidectomy and Tetany on Liver Cell Permeability

Following the removal of a parathyroid adenoma certain effects may result which are most worthy of recollection Underhill and Beatherwich [1] demonstrated that when two parathyroid glands are removed in dogs they

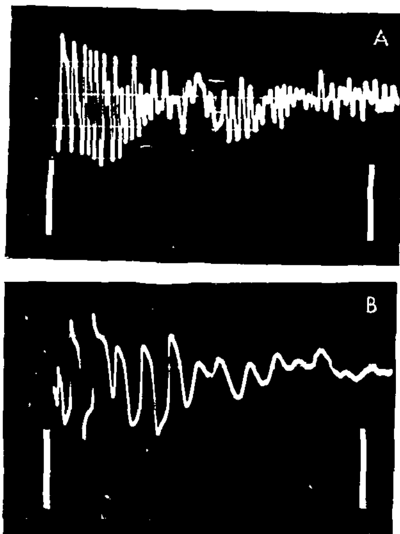


Fig 150 A Oscillographic reproduction of the percussion notes of the skull of a normal adult *B* Frequency of the abnormal note in a patient with hyperparathyroidism in whom the so called "watermelon sign" was elicited The frequency of a normal note is approximately 2600 per second The frequency of the abnormal note is approximately 800 per second (Fender F A Diagnostic sign in hyperparathyroidism J A M A **154** March 17 1954)

From the point of view of surgical technique, it is well to remember that the parathyroid glands are very small As a matter of fact they have been described as being about the size of an orange seed Cowdry [47] and Biedl [49] measured the parathyroid gland in many anatomical specimens and their measurements were

of more than one mass should lead one to suspect the presence of carcinoma of the parathyroid gland. In addition, invasion of the recurrent laryngeal nerve is a strong indication that the lesion is malignant. The parathyroid cancer is usually three times larger than the usual hyperfunctioning benign adenoma. Adenoma is found in the region of the lower pole of the right or

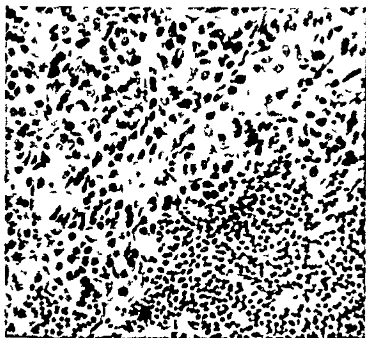


FIG 131 Photomicrograph (× 260) of a parathyroid tumor removed from a [illegible] year old housewife. This section shows both a benign and a malignant tumor. This is evidence for malignancy developing in a previously benign adenoma. Note the difference in size, shape and arrangement between the larger carcinomatous and the smaller adenomatous cells. (Cope, O: Surgery of hyperparathyroidism. Ann Surg 114: 706, 1941.)

left thyroid lobe is a more common location for malignant lesions than those found in the upper poles.

When the specimen is examined in the laboratory, certain findings indicate carcinoma of the parathyroid gland. However, the usual pathological criteria cannot always be applied to the parathyroid gland. For example, cellular pleomorphism, giant nuclei, nests of tumor cells in blood vessel or apparent invasion of the capsule are not sufficient evidence in the differential diagnosis of parathyroid tumors. The presence of mitotic figures, a trabecular pattern, tumor thrombi and lymphatic invasion, however

develop a marked drop in the blood sugar level When these animals were sacrificed 4 days after parathyroidectomy it was found that the liver lost its entire glycogen content There was also an elevation in the blood sugar during the 4 days after parathyroidectomy When an injection of calcium lactate was given intravenously the blood sugar returned to a normal level and the symptoms of tetany which were in evidence were abolished These investigators believe that in parathyroidectomized animal due to the calcium deficiency their livers lost glycogen resulting in a hypoglycemia Therefore when this deficiency is corrected by means of the calcium lactate, the liver recovers its storage capacity and the blood sugar returns to a normal level

Removal of the parathyroid glands, experimentally, causes hypocalcemia This fall in blood serum calcium is followed by an increase in cell membrane permeability The parathyroid hormone in the intact animal mobilizes calcium from the bones in order to maintain the normal level of calcium in the blood serum With the removal of the parathyroid glands the loss of calcium from the circulation cannot be replaced and hypocalcemia results which leads to the loss of cell membrane semipermeability

From a cardiac point of view certain changes may occur in the electrocardiogram following parathyroidectomy The loss of calcium interferes with the conduction time of the heart and the R T interval is altered These changes are temporary and can easily be corrected by the administration of calcium

Following parathyroid surgery it is possible that the patient does not have a satisfactory clinical improvement If laboratory studies are performed and continued, high serum calcium persists in spite of the removal of one or two parathyroid adenomata This laboratory finding indicates that remaining adenomatous tissue is present in the patient Thought should then be given to a second operation with the possibility that another parathyroid adenoma is in an ectopic location

Carcinoma of the Parathyroid Gland

The interpretation of parathyroid carcinoma as of now, is at the stage of indecision similar to the state of affairs in reference to thyroid cancer several decades ago For this reason the diagnosis of parathyroid carcinoma can be intimated more accurately at the operating table than under the microscope

At the time of surgery the diagnosis may be strongly suspected from the gross appearance of the adenomatous lesion This is especially valuable when a frozen section may be more confusing than revealing For example, local invasion of surrounding tissue metastatic implants, or the presence

Bibliography

1 Zondek H Quoted by Hergert R *See also reference* 236
2 Means J H The Thyroid and Its Diseases Philadelphia J B Lippincott Co 1937
3 Lahey F H Acute hyperthyroidism (thyroid crises) New York State J Med 33 837 1933
4 Crile G W Jr Important factors in the surgical management of patients with severe hyperthyroidism South Surg 11 282 1942
5 Hergert R Origin and prevention of hyperthyroid coma Chirurg 12 417 1940
6 Foss H L Hunt H F and McMillan R The pathogenesis of crisis and death in hyperthyroidism J A M A 113 1090 1939
7 McGregor J K Hyperthyroid crisis West J Surg Obst & Gynec 49 367 1941
8 Nash J Surgical Physiology Baltimore Charles C Thomas 1942
9 Levy R L Studies on the conditions of activity in endocrine glands IV The effect of thyroid secretion on action of adrenin Am J Physiol 41 492–511 1916
10 Rienhoff W F Diseases of Thyroid Gland In Practice of Surgery VI Ed Lewis D and Walter W Hagerstown W F Prior Co 1936
11 Goetsch E Studies on disorders of the thyroid gland Hypersensitiveness test with especial reference to diffuse adenomatosis of the thyroid gland Endocrinol 4 389–402 1920
12 — and Ritzmann A J Jr Thyroid disorders VI The suprarenal factor in reactions to thyroidectomy Arch Surg 29 492–510 1934
13 Means J H Diagnosis and treatment of Hyperthyroidism Canad M A J 43 509–513 1940
14 Maddock W G Coller F A and Pedersen S Thyroid crisis its relation to liver function and adrenalin West J Surg 44 513–521 1936
15 Rea C E The treatment of thyroid crisis Minnesota Med 25 368 1942
16 Brace D F and Reid C L The use of ergotoxine and ergotamine in the surgical management of thyrotoxicosis Ann Surg 113 62 1941
17 Lahey F H Critical thyroid state diagnosis and treatment Surg Clin North America 16 1521–1531 1936
18 Ewald W Results of treatment in exophthalmic goiter Deutsche Ztschr f Chir 239 275 1933
19 Litchford J K The significance of the postoperative thyroid reaction Canad M A J 32 163 1935
20 Schneider E Concerning the broadening of the indications for operation in exophthalmic goiter through the recognition at the bedside of a secondary thyrogenic injury to the liver Internat Clin 2 87–98 1934
21 Pedersen S Maddock W G and Coller F A Serum sodium in relation to liver damage and hyperthyroidism Proc Soc Exp Biol 36 491 1937
22 Maddock W G et al Studies of blood chemistry in thyroid crisis J A M A 109 2130–35 1937
23 Schryver S B Quoted by Weller Hepatic lesions associated with exophthalmic goiter Tr Ass Am Physicians 45 71–75 1930
24 Farrant R Hyperthyroidism Its experimental reproduction in animals Brit M J 2 1363–1367 1913

must be considered as adequate signs on microscopic examination, that carcinoma of the gland is present

Patients with parathyroid cancer are usually found in the early forty's They are, therefore younger than patients with adenomata Although adenomata are more commonly found in women the presence of parathyroid cancer is equally distributed in both men and women

As previously stated surgery is indicated for parathyroid carcinoma as well as benign adenoma All tumor tissue must be removed at the time of operation Removal of the thyroid lobe on the side involved with sacrifice of the recurrent laryngeal nerve may be necessary The presence of metastatic involvement either to regional lymph nodes or contiguous structures demands that a radical neck dissection be performed The utility of irradiation or radioactive iodine is problematical in parathyroid carcinoma There is no objection to irradiation especially when complete excision of the tumor cannot be performed

Prognosis in parathyroid carcinoma is not very promising Black [10] states that 16 or 20 patients with parathyroid cancer reported in the literature are now dead However surgical intervention relieved the symptomatology for an average of 20 months even in those patients with known metastases The recurrence of the tumor is quite high and death is almost inevitable within 2 years if invasion of the tumor is macroscopically demonstrated at the time of surgery

48 MARUNO Y Experimental studies on halogen excretion from the liver On excretion of bromine and iodine from the liver J Gastroenterol Dis 3 9 1931

49 YUZURIHA T Iodine metabolism with particular reference to the significance of the role played by the reticulo-endothelial system J Chosen Med As 25 1059 1271 1498 1535

50 DE COURCY J L Iodine content of blood in cholecystic disease Arch Surg 35 140–47 1937

51 BOYCE F AND MCFETRIDGE E M Studies of hepatic function by the Quick hippuric acid test II thyroid disease Arch Surg 37 427 1938

52 CONNELL F G Liver death Rapid high temperature death Ann Surg 100 319–27 1934

53 CRILE G W AND CRILE G W JR Individualization of the patient in the treatment of hyperthyroidism Cleveland Clin Quart 2 23–6 1935

54 DINSMORE R S Factors influencing morbidity in thyroid surgery J A M A 109 179–183 1937

55 — AND HARRI I E Management of complications and emergencies in thyroid surgery Surg Clin North America 17 1529–1540 1937

56 LAHEY F H Reduction of mortality in hyperthyroidism New England J Med 213 4 5–419 1935

57 LORD J W AND ANDRUS W DEW Changes in the liver associated with hyperthyroidism with a study of plasma prothrombin levels in the immediate post operative period Arch Surg 42 643–660 1941

58 FRAZIER C H AND NORTH J P Carbohydrate metabolism in hyperthyroidism 1933 Annual Session Tr Am A Study Goiter pp 203–209

59 FRAZIER C H AND BROWN R B The thyroid and the liver West J Surg 43 636–646 1935

60 FRAZIER W D AND FRIEMAN H Alterations in liver glycogen following thyroid iodine and glucose feedings Surg Gynec & Obst 60 27–29 1935

61 — AND RAVDIN I S The use of vitamin B in the preoperative preparation of the hyperthyroid patient Surgery 4 680–686 1938

62 BARTLETT W JR Effects upon blood amylase of variations in thyroid activity Proc Soc Exper Biol & Med 36 843–848 1937

63 — Role of the liver in thyrotoxicosis Surgery 3 261–262 1938

64 PERRAZZO Quoted by BOYCE F F See reference 42

65 SHAFFER J M Disease of the liver in hyperthyroidism Arch Path 29 0 1940

66 WEBSTER B AND CHESNEY A M Studies in etiology of simple goiter A M A J Path 6 275–284 1930

67 MARINE D Cited by BOYD W See reference 68

68 BOYD W Surgical Pathology Philadelphia W B Saunders Co 1943

69 ASHER L AND DURAN M Beitrage Zur Physiologie der Drusen XLIV Das Verhalten von normalen mit Schilddrusensubstanz gefutterten und schilddrusen losen Ratten gegen reinem Sauerstoffmangel Biochem Ztschr 106 254 1920

70 STRELLI H AND ASHER L Beitrage zur physiologie der Drusen XXXVI Das Verhalten von schilddrusenlosen milzlosen schilddrusen und milzlosen Tieren bei O-Mangel Zugleich ein Beitrag Zur Theorie der Bergkrankheit Biochem Ztschr 87 359 1918

71 BEST C H AND TAYLOR N B The Physiological Basis of Medical Practice 2nd Ed Baltimore Williams & Wilkins Co 1940 p 468

72 REINWEIN H AND SINGER W Studien uber die Gewebsatmung IV Der

25 CRAMER AND KRAUSE Cited by WELLER C V *See reference 38*

26 KURIYAMA S Influence of thyroid feeding upon carbohydrate metabolism Am J Physiol 43 181–196 1917

27 — Influence of thyroid feeding upon carbohydrate metabolism I Storage and mobilization of liver glycogen in thyroid fed animals J Biol Chem 33 193–205 1918

28 HASHIMOTO H The heart in experimental hyperthyroidism with special reference to its histology Endocrinol 5 597–606 1921

29 GOODPASTURE E W The influence of thyroid products on the production of myocardial necrosis J Exper Med 34 407 1921

30 — Myocardial necrosis in hyperthyroidism J A M A 76 1545–1551 1921

31 HABAN G Leberveranderungen bei experimentellem Hyperthyreoidismus Beiter z path Anat u z allge Path 95 573–589 1935

32 ZELDENRUST J AND VAN BEEK C C Morphologic and experimental contribution to the pathogenesis of hepatic change in exophthalmic goiter Neder tijd chr v genee k 83 889 1939

33 CAMERON G R AND KARUNARATNE W A Liver changes in exophthalmic goiter J Path Bact 41 267–282 1935

34 ROESSLE R Uber der veranderung der Leber bei der basedowischen Krankheit und ihre bedeutung fur die entstehung anderer organ Klerosen Virch Archiv 291 1 1933

35 PARTURIER G AND DELFRUE J Les syndromes hepato-thyroidiens Rev med chir de mal du foie 9 331–87 1934

36 ROWE A W Endocrine studies XXXV The association of hepatic dysfunction with thyroid failure Endocrinol 17 1–22 1933

37 BEAVER D C AND PEMBERTON J The pathologic anatomy of the liver in exophthalmic goiter Ann Int Med 7 687 1933

38 WELLER C V Hepatic pathology in exophthalmic goiter Ann Int Med 7 543 1933

39 YOUMANS J B AND WARFIELD L M Liver injury in thyrotoxicosis as evidenced by decreased functional efficiency Arch Int Med 37: 1–17 1926

40 ASSMANN H Cited by WILENSKY A D Occurrence distribution and pathogenesis of so-called liver death and for the hepatorenal syndrome Arch Surg 38 625–691 1939

41 MAHORNER H R Jaundice associated with hyperthyroidism New Orleans M S J 87 382 1934

42 BOYCE F F The Role of the Liver in Surgery Baltimore Charles C Thomas 1941

43 JUDD E S The physiology of the liver and its relation to surgery of the biliary tract (Trimble Lecture) Ann Surg 90 1035–45 1929

44 PICKHARDT O C BERNHARD A AND KAHN I I The significance of the cholesterol partition of the blood serum in surgery of the gallbladder Ann Surg 110 701–722 1939

45 SPERRY W M Relationship between total and free cholesterol in human blood serum J Biol Chem 114 125–133 1936

46 BARTELS F C Serum protein studies in hyperthyroidism New England J Med 218 283–294 1938

47 COHN A AND FELDMAN S E Relation between liver and thyroid gland blood iodine as indicator of liver function Am J Clin Path 12 27–31 1942

48 MARENO V Experimental studies on halogen excretion from the liver On excretion of bromine and iodine from the liver J Gastroenterol Dis 3 97 1931
49 YUZURIHA T Iodine metabolism with particular reference to the significance of the role played by the reticulo-endothelial system J Chosen Med Ass 25 1059 1? 1 1198 1935
50 DE COURCY J L Iodine content of blood in cholecystic disease Arch Surg 35 140-147 1937
51 BOYCE F AND McFETRIDGE E M Studies of hepatic function by the Quick hippuric acid test II thyroid disease Arch Surg 37 427 1938
52 CONNELL F G Liver death Rapid high temperature death Ann Surg 100 319-?7 1934
53 CRILE C W AND CRILE G W JR Individualization of the patient in the treatment of hyperthyroidism Cleveland Clin Quart 2 23-56 1935
54 DINSMORE R S Factors influencing morbidity in thyroid surgery J A M A 109 179-183 1937
55 — AND HARRIS L E Management of complications and emergencies in thyroid surgery Surg Clin North America 17 1529-1540 1937
56 LAHEY F H Reduction of mortality in hyperthyroidism New England J Med 213: 475-479 1935
57 LORD J W AND ANDRUS W DEW Changes in the liver associated with hyperthyroidism with a study of plasma prothrombin levels in the immediate post operative period Arch Surg 42 643-660 1941
58 FRAZIER C H AND NORTH J P Carbohydrate metabolism in hyperthyroidism 1933 Annual Session Tr Am A Study Goiter pp 203-209
59 FRAZIER C H AND BROWN R B The thyroid and the liver West J Surg 43 656-646 1935
60 FRAZIER W D AND FRIEMAN H Alterations in liver glycogen following thyroid iodine and glucose feedings Surg Gynec & Obst 60 27-29 1935
61 — AND RAVDIN I S The use of vitamin B in the preoperative preparation of the hyperthyroid patient Surgery 4 680-686 1938
62 BARTLETT W JR Effects upon blood amylase of variations in thyroid activity Proc Soc Exper Biol & Med 36 843-848 1937
63 — Role of the liver in thyrotoxicosis Surgery 3 261-262 1938
64 PERRAZZO Quoted by BOYCE F F See reference 4?
65 SHAFFER J M Disease of the liver in hyperthyroidism Arch Path 29 20 1940
66 WEBSTER B AND CHESNEY A M Studies in etiology of simple goiter A M A J Path 6 275-281 1930
67 MARINE D Cited by BOYD W See reference 68
68 BOYD W Surgical Pathology Philadelphia W B Saunders Co 1943
69 ASHER L AND DURAN M Beitrage Zur Physiologie der Drusen XLIV Das Verhalten von normalen mit Schilddrusensubstanz gefutterten und schilddrusen losen Ratten gegen reinem Sauerstoffmangel Biochem Ztschr 106 254 1920
70 STREULI H AND ASHER L Beitrage zur physiologie der Drusen XXXVI Das Verhalten von schilddrusenlosen milzlosen schilddrusen und milzlosen Tieren bei O_2-Mangel Zugleich ein Beitrag Zur Theorie der Bergkrankheit Biochem Ztschr 87 359 1918
71 BEST C H AND TAYLOR N B The Physiological Basis of Medical Practice 2nd Ed Baltimore Williams & Wilkins Co 1940 p 468
72 REINWEIN H AND SINGER W Studien uber die Gewebatmung IV Der

Einfluss von Thyroxin adrenalin und Insulin auf den Sauerstoffverbauch uberlebender Leberzellen Biochem Ztschr., 197 152 1928

73 McIver M A and Winter E A Increased susceptibility to chloroform poisoning produced in rats by injection of crystalline thyroxin Proc Soc Exper Biol Med 45 201 1940 J Clin Invest 21 191 1942

74 — and — Deleterious effects of anoxia on the liver of the hyperthyroid animal Arch Surg 46 171-185 1943

75 Lewis R A Thorn C W Koepf C F and Dorrance S S The role of the adrenal cortex in acute anoxia J Clin Invest 21 33 1942

76 Evans C The effect of low atmospheric pressure on the glycogen content of the rat Am J Physiol 110 273 1934

77 — The adrenal cortex and endogenous carbohydrate formation Am J Physiol 114 297 1936

78 Farrant R Hyperthyroidism Its experimental production in animals Brit M J 2 1363 1913

79 Gerlei I Necrose due foie consecutive a l'empoisonnement par la thyroxine Ann d anat path 10 555 1933

80 Haban C Leberveranderungen bei experimentellem Hyperthyreoidismu Beitr z path Anat u z allg Path 95 573 1935

81 Colcock B A review of the pathogenesis and surgical treatment of thyroid disease Surgery 10 356-357 1941

82 Cole W H and Brunner R Anesthesia in thyroidectomy for thyrotoxicosis Surg Gynec & Obst 70 211 1940

83 Schnedorf J G McClure R D and McGraw A B Rationale and use of oxygen in the postoperative treatment of hyperthyroidism Quoted by Colcock *See reference* 81

84 Haines S F and Boothby W M Oxygen treatment with special reference to treatment of complications incident to goiter Am J Surg 7 174 1929

85 Bartels E C and Kingsley J W Hyperthyroidism with myasthenia gravis Lahey Clinic Bulletin 6 4 1949

86 Black B M and Haynes A L Intrathyroid parathyroid adenoma Proc Staff Mayo Clinic 24 16 1949

87 Cope O Disease of thyroid gland New England J Med 246 368-437 1952

88 Crotti A A study based on forty-one years of thyroid surgery J Internat Coll Surgeon 13 550 1950

89 Ficarra B J and Nacleiro E Thyroid crisis Pathogenesis of hepatic origin Am J Surg 69 325 1945

90 — Psychosomatic symptoms and borderline hyperthyroidism Am J Surg 71 363-364 1946

91 Lahey F H and Ficarra B J Aberrant thyroid Surg Gynec & Obst 82 705-711 1946

92 Ficarra B J Struma lymphomatosa A.M.A. Arch Surg 52 729-736 1946

93 — and Nelson R A Phobia as a symptom in hyperthyroidism Am J Psychiat 103 831-832 1947

94 — Elective tracheotomy following thyroidectomy New York State J Med 48 919-920 1948

95 — Use and abuse of antithyroid drug New York State J Med 49 1055-1056 1949

96 deRoberti E Treatment of hyperthyroidism III Radioactive iodine J.A.M.A. 139 10 1949

97 Lahey F H Technique of thyroidectomy Surgery 16 05-724 1944
98 Thosek I Fallacy of so-called thyroid capsule Am J Surg 77 133-138 1949
99 Murphy R Hyperparathyroidism Lahey Clinic Bull 6 4 1949
100 Lahey F H Surgery of the Thyroid gland New England J Med 236 46-62 1947
101 Ficarra B J Thyroid disease and the climacterium Med Time 77 411-413 1949
102 — Clinicopathologic study of 100 consecutive thyroid procedures J Internat Coll Surgeons 13 41-44 1950
103 — Observations on thyroid disease Med Times 78 292-296 1950
104 — Tiroidectomia en la Compresion Traqueal del Adults J Internat Coll Surgeons (Spanish Ed) 1950
105 — Transient cardiac arrhythmia following thyroidectomy New York State J Med 50: 1816 1950
106 — Life history of a patient treated with radioactive iodine Med Times 78 583-584 1950
10 — Hyperthyroidism before puberty Med Time 79 284-286 1951
108 — Thyroid enlargement due to hemorrhage New York State J Med 51 1554 1951
109 — Thyroid surgery in the elderly Geriatrics 6 251-252 1951
110 — Hyperthyroidism and pregnancy Med Times 79 752-753 1951
111 — Thyroid disease Pain as a symptom in thyroid disease (Apathetic hyperthyroidism) Med Time 80 236-237 1952
112 — Hurthle cell adenoma of thyroid New York State J Med 52 116 1952
113 — Practical aspects of thyroidectomy New York State J Med 53 215-217 1953
114 — Present day physiology and management of hyperthyroidism New York State J Med 53 98-980 1953
115 Thorn G W and Eder H A Studies on chronic thyrotoxic myopathy Am J Med 1 583-601 1946
116 Summers D Hurthle cell adenoma Arch Path 31 99 1941
117 Wilensky A O and Kaufman P H Hurthle cell tumor of the thyroid gland Surg Gynec and Obst 1 10 1938
118 Foulger M I and Rose F Acute goiter during thiocyanate therapy of hypertension J A M A 122 1072 1943
119 Barr D P Thyroiditis and myxedema Bull New York Acad Med 29 551-569 1953
120 De Quervain F Die akute nicht eitrige thyreoiditis Mitt Grenzgeb Med Chir Supplement 2 1904
121 — and Giordanego G Die akute und subakute nicht-eitrige Thyreoiditis Mitt Grenzgeb Med Chir 44 538-590 1936
122 Crile G W Jr and Hazard J B Classification of thyroiditis with special reference to the use of needle biopsy J Clin Endocrin 11 1123-1127 1951
123 — Thyroiditis Diagnosis and therapy Ann Int Med 37 519-524 1952
124 Case records of the Massachusetts General Hospital B Castleman Ed New England J Med 246 704-710 1952
125 Warner S C Quimby E H and Schmidt C The use of tracer doses of radioactive iodine I in the study of normal and disordered thyroid function in man J Clin Endocrinol 9 342-354 1949
126 Hamilton E Dirkendall M M and Barker S B Radioactive iodine uptake

Einfluss von Thyroxin adrenalin und Insulin auf den Sauer toffverbauch uberlebender Leberzellen Biochem Ztschr 197 152 1928
73 McIver M A and Winter L A Increased susceptibility to chloroform poisoning produced in rats by injection of crystalline thyroxin Proc Soc Exper Biol Med 45 201 1940 J Clin Invest 21 191 1942
74 — and — Deleterious effects of anoxia on the liver of the hyperthyroid animal Arch Surg 46 171–185 1943
75 Lewis R A Thorn G W Kolff G F and Dorrance S S The role of the adrenal cortex in acute anoxia J Clin Invest 21 33 1942
76 Evans C The effect of low atmo pheric pressure on the glycogen content of the rat Am J Physiol 110 273 1934
77 — The adrenal cortex and endogenous carbohydrate formation Am J Physiol 114 297 1936
78 Farrant R Hyperthyroidi m Its experimental production in animals Brit M J 2 1363 1913
79 Gerlei I Necrose due foie con ecutive a l'empoisonnement par la thyroxine Ann d anat path 10 555 1933
80 Haban C Leberveranderungen bei experimentellem Hyperthyreoidi mus Beitr z path Anat u z alleg Path 95 573 1935
81 Colcock B A review of the pathogenesis and surgical treatment of thyroid disea e Surgery 10 336–357 1941
82 Cole W H and Brunner R Anesthesia in thyroidectomy for thyrotoxico is Surg Gynec & Ob t 70 211 1940
83 Schnedorf J G McClure R D and McGraw A B Rationale and use of oxygen in the po toperative treatment of hyperthyroidism Quoted by Colcock See reference 81
84 Haines S F and Boothby W M Oxygen treatment with special reference to treatment of complications incident to goiter Am J Surg 7 174 1929
85 Bartels L C and Kingsley J V Hyperthyroi lism with myasthenia gravis Lahey Clinic Bulletin 6 4 1949
86 Black B M and Haynes A L Intrathyroid parathyroid adenomas Proc Staff Mayo Clinic 24 16 1949
87 Cope O Diseases of thyroid gland New England J Med 246 368–457 1952
88 Crotti A A study based on forty one years of thyroid surgery J Internat Coll Surgeon 13 530 1950
89 Ficarra B J and Naclerio E Thyroid cri is Pathogene is of hepatic origin Am J Surg 69 325 1945
90 — Psycho omatic symptoms and borderline hyperthyroidi m Am J Surg 71 563–364 1946
91 Lahey F H and Ficarra B J Aberrant thyroid Surg Gynec & Obst 82 705–711 1946
92 Ficarra B J Struma lymphomatosa A M A Arch Surg 52 729–736 1946
93 — and Nelson R A Phobia as a symptom in hyperthyroidi m Am J Psychiat 103 831–832 1947
94 — Elective tracheotomy following thyroidectomy New York State J Med 48 919–920 1948
95 — Use and abuse of antithyroid drug New York State J Med 49 1055–1056 1949
96 deRobertis E Treatment of hyperthyroidi m III Radioactive iodine J A M A 139 10 1949

156 CHANCE D P DEVINE K D AND SCHMIDT H W Cicatricial tracheal stenosis after tracheotomy Report of a case Proc Staff Meet Mayo Clinic **29** 388 342 1954
157 BUXTON C L AND HERRMANN W L Effect of thyroid therapy on menstrual disorders and sterility J A M A **155** 1035–1039 1954
158 CHINSKY M Evaluation of methods for determining basal metabolic rate in office practice J A M A **155** 1055–1057 1954
159 FROHNER R N AND WOLGAMOT J C Primary hyperparathyroidism 5 cases in *one family* Ann Int Med **10** 765–773 1954
160 CHESKY V E DREESE W C AND HELLWIG C A Chronic thyroiditis Review of 42 cases J Internat Coll Surgeons **21** 679–700 1954
161 MORGANS M E AND TROTTER W R Treatment of thyrotoxicosis with potassium perchlorate Lancet **1** 749–751 1954
162 CHESKY V E DREESE W C AND HELLWIG C A Invasive adenoma of the thyroid Surg Gynec & Obst **98** 581 1954
163 HAINE S T Treatment of exophthalmic goiter New York State J Med **54** 2175–2179 1954
164 HELLWIG C A Colloidophagy in the thyroid gland A M A Arch Path **58** 151–152 1954
165 TANABE H AND WAKABAYASHI M Colloidophagy in the human thyroid gland Tr Soc Path Japan **30** 913 1940
166 BUNO W Estudios de histofisiopatologia tiroidea Buenos Aires El Ateno 1943
167 HELLWIG C A Colloidophagy in the human thyroid gland Science **113** 725 1951
168 LOEB L AND BASSETT R B Comparison of effect of various preparations of anterior pituitary gland on thyroid of guinea pig Proc Soc Exper Biol & Med **27** 490 1930
169 THURSTON E W A comparison of hypertrophic changes in thyroid caused in different species by acid extract of the anterior lobe of the bovine pituitary gland Arch Path **15** 67 1933
170 EGGERT B Morphologie und Histophysiologie der normalen Schilddruse Leipzig Johann Ambrosius Barth 1938
171 WILLIAMS R G Some properties of living thyroid cell and follicles Am J Anat **75** 95 1944
172 MORTON M E AND SCHWARTZ J R The stimulation in vitro of phospholipid synthesis in *thyroid tissue by thyrotropic hormone* Science **117** 103 1953
173 DOBYNS B M Studies on exophthalmos produced by thyrotropic hormone Surg Gynec & Obst **82** 717 1946
174 FERGUSON J A Tissue reaction to colloid and lipoids from human thyroid gland Arch Path **15** 244 1933
175 PEARLMAN I N Goiter in a premature infant Canadian Med A s J **70** 317–319 1954
176 WALTON R L Neonatal tetany in two siblings Effect of maternal hyperparathyroidism Pediatrics **13** 227–234 1954
177 LAMBERG B A The Thyrohypophysial Syndrome I The primary reaction of the hypophysial eye signs (including exophthalmos) to the treatment of thyrotoxicosis Acta Med Scandinav **148** 225–237 1954
178 GROSS J AND LEBLOND C P Metabolites of thyroxine Proc Soc Biol & Med **76** 686 1951
179 — AND PITT RIVERS R Unidentified iodine compounds in human plasma in

of the thyroid and plasma protein bound iodine in subacute thyroiditis J Clin Invest 29 819–829 1950
127 Price I W Histology of thyroid gland Med Illust Feb 1949
128 Graham L A Surgical Diagnosis Phil W B Saunders Co 1950
129 Shapiro P F Metastasis of the thyroid tissue to abdominal organ with special case report of struma ovarii metastasing to omentum Ann Surg 92 1031–1042 1930
130 Ulrich H F Lingual thyroid Ann Surg 95: 503 1932
131 Churchill E and Allen A W In Means J H Thyroid and Its Diseases Philadelphia J B Lippincott Co 1937
132 Story H and Bolker H An unusual location of an aberrant thyroid Laryngoscope 44 926 1934
133 Wynne H M McCartney J S and McClendon J F Struma ovarii Am J Obst & Gynec 39 263 1940
134 Hartley J N J Some errors in the development of the thyroid gland Surg Gynec & Obst 35 543 1922
135 Novak E Gynecological and Obstetrical Pathology Philadelphia W B Saunders Co 1941
136 Plaut A Struma of ovary Arch Path 10 161 1930
137 Klefine H O Die Sogenannte Struma Ovarii Arch F Gyn 158 62 1934
138 Kovacs F Uber die Schilddrusengeschwulst des Ovariums Arch F Gyn 122 66 1924
139 Ward C F Hendrick J W and Chambers R G Thyroglossal tract abnormalities Surg Gyne & Obst 89 727 1949
140 Seven M J and Perloff W H Post thyroidectomy thyroid crisis J Phila delphia Gen Hosp 4 3–9 1953
141 Jackson A Complication following thyroidectomy In Ficarra B J Emergency Surgery Philadelphia F A Davis Co 1953
142 Walsh F B Myasthenia gravis and its ocular sign Tr Am Oph Soc 41 556 1943
143 Castleman B Pathology of the thymus in myasthenia gravis Medicine 28 27 1949
144 Buckwalter J and Layton J Malignant teratoma in the thyroid gland of an adult Ann Surg 139 218 223 1954
145 McClintock J C Stranahan A Alley R D and Baker W A Thoraco cervical approach for malignant disease of thyroid Ann Surg 139 158–165 1954
146 Iason A Thyroid Gland in Medical History New York Froben Press 1946
147 Levitt T The Thyroid London E and S Livingstone Ltd 1954
148 Fender F A Diagnostic sign in hyperparathyroidism J A M A 154 1085–1086 1954
149 Black B M Hyperparathyroidism Springfield Charles C Thomas 1953
150 Hobler R E Hyperparathyroidism New York State J Med 54 1457–1462 1954
151 Shelling D H The parathyroids in health and disease St Louis C V Mosby Co 1935
152 Mandl F Arch Fur Klin Chir 143 245 1926
153 Albright F Aub J C and Bauer W Hyperparathyroidism J.A.M.A 102 1276 1934
154 Symposium on Exophthalmos California Med 80 72–79 1954
155 Ward G E Cantrell J R and Allan W B The surgical treatment of lingual thyroid Ann Surg 139 536–546 1954

202 Gross J and Pitt Rivers R Unidentified iodine compound in human plasma Lancet 261: 766–67 1951
203 — Identification of 3 5 3 L-Triiodothyronine in human plasma Lancet 1 439–441 1952
204 — Physiological activity of 3 5 3 L Triiodothyronine Lancet 1 593–594 1952
205 — Pitt Rivers R and Trotter W R Effect of 3 5 3 L Triiodothyronine in myxedema Lancet 1 1044–1045 1952
206 Libby D A, and Meites J Negative effects of antibiotics on thyroid gland Science 120 354 1954
207 Rinkoff S Freid J R Rosman I and Spring M Treatment of hyperthyroidism with radioactive iodine New York State J Med 54 2480–2473 1954
208 Jackson A S Intrathoracic goiters Bull Jackson Memorial Hosp 16 48–56 1954
209 Nordland M and Nordland M A Evaluation of surgical treatment for disturbances of the thyroid gland A M A Arch Surg 68 94–99 1954
210 Black B M Carcinoma of the parathyroid Ann Surg 139 355–62 1954
211 Pemberton J De J and Black B M Cancer of thyroid Monograph of American Cancer Society 1954
212 Albright F and Reifenstein E C Jr The Parathyroid Glands and Metabolic Bone Disease Baltimore Williams & Wilkins Co 1948
213 Attie J N and Leblmutter M Diagnosis and treatment of hyperparathyroidism New York State J Med 54 2417–2423 1954
214 Carter Frances Adrenocortical function in hypo and hyperthyroidism Proc Soc Exper Biol & Med 86 660–63 1954
215 Contopoulos A Evans E S Ellis S and Simpson M Increased metabolic rate without thyroid participation on injection of rat with pituitary erythropoietic fractions Proc Soc Exper Biol & Med 86 729–433 1954
216 Weiss S B Henkin C and Marx W Cholesterol balance studies in mice with modified thyroid activities Proc Soc Exper Biol & Med 86 800–803 1954
217 Blackburn C R B Management of chronic hypoparathyroid tetany M J Australia 1 928–32 1954
218 Duffy B J Jr Wheeler T E Novak P J and Howard H N Comparison of thyroid function test U S Armed Forces M J 5 995–9 1954
219 Salvesen H A Relationships between parathyroids and bone diseases Minerva Medicina (Turin Italy) 45 1473–76 1954
220 Madigan J P and King W B Radio active iodine and protein bound Iodine in thyroid disorders M J Australia 1 801–814 1952
221 Friedman G J Greenberger M E and Brandaleone H Hyperparathyroidism with severe nephrocalcinosis J A M A 156 557–599 1954
222 World Goiter Survey Iodine Facts Iodine Education Bureau Stone House Bishop gate London E C 2 1954
223 Perinetti H Yaceofano C A Staneglone L and Nora J Medical-surgical experience with goiter in an endemic district Tr Am A Study Goiter 12–24 1952
224 Perinetti H and Freneau J El bocio en las Escuelas Provinciales y su profilaxes J Med Mendoza 11 1941
225 Chaikoff I L and Taurog A Studies on the formation of organically bound iodine compounds in thyroid gland Ann New York Ac Sciences 50 377–407 1949
226 Lardlaw J C Nature of the circulating thyroid hormone Nature 164 927–28 1949

addition to thyroxine and iodide Lancet 2 766 1951 The Identification of 3 5 3 L-Triiodothyronine in Human Plasma Lancet 1 439 1952
180 — AND — 3 5 3 Triiodothyronine 1 Isolation from thyroid gland and synthesis Biochem J 53 645 1953
181 — AND — (a) *Physiological activity of 3 5 3 L-Triiodothyronine Lancet 1* 593 1952 (b) 3 5 3 Triiodothyronine 2 Physiological Activity Biochem J 53 652 1953
182 TOMICH L G AND WOOLLETT E A The biological activity of triiodothyronine Lancet 1 726 1953
183 HEMING A E AND HOLTKAMP D L Comparative effects of thyroxine and triiodothyronine on oxygen consumption of rats Fed Proc 12 330 1953
184 GEMMILL C L Comparison of activity of thyroxine and 3 5 3 Triiodothyronine *Am J Physiol 172 286 1953*
185 GROSS J PITT RIVERS R AND TROTTER W R Effects of 3 5 3 L-Triiodothyronine in myxedema Lancet 1 1044 1952
186 ASPER S P SELENKOW H A AND PLAMONDON C A A Comparison of the metabolic activities of 3 5 3 L Triiodothyronine and L-Thyroxine in myxedema Bull Johns Hopkins Hosp 93 164 1953
187 RAWSON R W RALL S E PEARSON O H ROBBINS J AND POPPELL H F L Triiodothyronine versus L-Thyroxine A comparison of their metabolic effects *in human myxedema Am J M Sc 226 405 1953*
188 LERMAN J The Physiological activity of L-Triiodothyronine J Clin Endocrinol 13 1341 1955
189 WILKINSON J H SEROTT W E BOWDEN C H AND MACLAGAN N F The biological action of substances related to thyroxine The effects of butyl 4 Hydroxy-3 5 Diiodobenzoate on the deiodination of diiodotyrosine and thyroxine in rats Biochem J 56 215 1954
190 DECOURCY J L AND DECOURCY C B Newer knowledge of thyroid pathology in terms of matrical theory Am J Surg 88 210–217 1954
191 THALMANN A Incidence of malignant goiter at the pathological Institute of Bern Switzerland between 1910 and 1950 and its relationship to iodine prophylaxis of endemic goiter Schweiz Med Wchnschr 84 473–4 8 1954
192 ALESSANDRI R Thyroid and parathyroid bone tumors without primary lesion of the thyroid gland Surg Gynec & Obst 45 35 1927
193 PIERI G Gli epiteliomi della tiroide e le lora metastasi nelle ossa Att d Clin Otorinolargingoiat d r Univ di Roma 13 150 1907
194 SAVIOZZI P Adenocarcinoma tiroideo pulsanti dell e tremo superiore dell omero Att d Clin Otorinolargingoiat d r Univ di Roma 13 476 1912
195 SIMPSON W Three cases of thyroid metastases to bones Surg Gynec & Obst 42 489 1926
196 ZAPELLONI L C Tumori epitchali primitivi delle ossa a tipo tiroideo e paratireoideo Tumori 2 5 1913
197 MEANS J H Lectures on the Thyroid Cambridge Harvard Univ Press 1954
198 STANBURY J B ET AL Endemic Goiter Cambridge Harvard Univ Press 1954
199 HARRIS R S MARRIAN G F AND THIMANN K V Vitamins and Hormones New York Academic Press Inc 1953
200 MADENBERG F BYFIELD G V AND BAKER L A Occurrence of ascites in myxedema A M A Arch Int Med 93 87 1954
201 CATLOW C E Mediastinal parathyroid adenoma West J Surg 62 552–553 1954

202 Gross J and Pitt Rivers R Unidentified iodine compounds in human plasma Lancet 261: 766–767 1951
203 — Identification of 3 5 3 L-Triiodothyronine in human plasma Lancet 1 439-441 1952
204 — Physiological activity of 3 5 3 L-Triiodothyronine Lancet 1 593 1952
205 — Pitt Rivers R and Trotter W R Effect of 3 5 3 L-Triiodothyronine in myxedema Lancet 1 1044-1045 1952
206 Libby D A and Meites J Negative effects of antibiotics on thyroid gland Science 120: 354 1954
207 Rinkoff S Freid J R Rosman L and Sirino M Treatment of hyperthyroidism with radioactive iodine New York State J Med 54 2470-473 1954
208 Jackson A S Intrathoracic goiters Bull Jackson Memorial Hosp 16 48-56 1954
209 Nordland M and Nordland M A Evaluation of surgical treatment of disturbances of the thyroid gland A M A Arch Surg 68 94 99 1954
210 Black B M Carcinoma of the parathyroid Ann Surg 139 355-62 1954
211 Pemberton J De J, and Black B M Cancer of thyroid Monograph of American Cancer Society 1954
212 Albright F and Reifenstein E C Jr The Parathyroid Glands and Metabolic Bone Disease Baltimore Williams & Wilkins Co 1948
213 Attie J N, and Perlmutter M Diagnosis and treatment of hyperparathyroidism New York State J Med 54 2717-2723 1954
214 Carter Frances Adrenocortical function in hypo and hyperthyroidism Proc Soc Exper Biol & Med 86: 660-63 1954
215 Contopoulos A Evans E S Lelli S and Simpson M Increased metabolic rate without thyroid participation on injection of rats with pituitary erythropoietic fractions Proc Soc Exper Biol & Med 86 729-733 1954
216 Weiss S B Henkin G and Marx W Cholesterol balance studies in mice with modified thyroid activities Proc Soc Exper Biol & Med 86 800-803 1954
217 Blackburn C R B Management of chronic hypoparathyroid tetany M J Australia 1 528-32 1954
218 Duffy B J Jr Wheeler T E Novak P J and Edwards H N Comparison of thyroid function tests U.S Armed Forces M J 5 995-9 1954
219 Salvesen H A Relationships between parathyroids and bone disease Minerva Medicina (Turin Italy) 45: 1473-76 1954
220 Madigan J P and King W B Radio active iodine and protein bound Iodine in thyroid disorders M J Australia 1 801-814 1952
221 Friedman G J Greenberger M E and Brandaleone H Hyperparathyroidism with severe nephrocalcinosis J A M A 156 537-539 1954
222 World Goiter Survey Iodine Facts Iodine Education Bureau Stone House Bishop gate London E C 2 1954
223 Perinetti H Yaceofano C A Stanelone L and Nora J Medical-surgical experience with goiter in an endemic district Tr Am A Study Goiter 12-27 1952
224 Perinetti H and Freneau J El bocio en las Escuelas Provinciales Y su profilaxes J Med Mendoza 11 1941
225 Chaikoff I L and Taurog A Studies on the formation of organically bound iodine compounds in thyroid gland Ann New York Ac Sc 50 357-402 1949
226 [illegible] Nature 164 927-28

227 KEATING F R JR HAINES S F POWER M H AND WILLIAMS M M D The Radioiodine—accumulating function of the human thyroid gland as a diagnostic test J Clin Endocrinol 10 1425–61 1950
228 VOGLIAZZO U VIOLE C SCORTA A AND MARCHIS F Valutazione della funzione tiroidea del cretinismo endemico Rassegna Clinica Scienza 28 3-13 1952
229 MEANS J H The thyroid hormone Bull Johns Hopkins Hosp 89 90–105 1951
230 TAUROG A CHAIKOFF I L AND TONG W The nature of plasma iodine as revealed by filter paper partition chromatography J Biol Chem 184 99 104 1950
231 WOLF J CHAIKOFF I L GOLDBERG R C AND MEIER J R The temporary nature of the inhibitory action of excess iodide on organ Iodine synthesis in the normal thyroid Endocrinology 45 504–13 1949
232 TAYLOR S The evolution of nodular goiter J Clin Endocrinol & Metab 13 1232–1247 1953
233 GROSS J AND PITT RIVERS R Recent knowledge of the thyroid gland In Vitamins and Hormones Harris R S et al Ed New York Academic Press Inc 1953
234 RAWSON R W GRAHAM R M AND RIDDELL C B Physiological reactions of the thyroid stimulating hormone of the pituitary II The effect of normal and pathological human thyroid tissues on the activity of the thyroid stimulating hormone Ann Int Med 19 405–414 1943
235 SALTER W T The Endocrine Function of Iodine Cambridge Harvard Univ Pres 1940
236 ZONDEK H Diseases of the Endocrine Gland 3rd Ed London E Arnold & Co 1935
237 BARTELS T D Heredity in Graves Diseases Copenhagen Munksgaard 1941
238 STANBURY J B BROWNELL C L RIGGS D S PERINETTI H DEL CASTILLO E AND ITOIZ J Adoption to Iodine Deficiency A Study of Endemic Goiter Cambridge Harvard Univ Press 1954
239 BABCOCK W W Multiple giant celled tumor of bone (Pagets) due to parathyroid tumor Surg Cl No Am 12 1387 1932
240 BALLIN M Clinical recognition and surgical treatment of parathyroidism Am J Surg 24 56 1934
241 BARR D P BULGER H A AND DIXON H H Hyperparathyroidism J A M A 82 951 1929
242 BROOKE R Generalized osteitis fibrosa Rapid recalcification of bone after complete parathyroidectomy Proc Roy Soc Med 28 1366 1935
243 COMPERE E L Role of the parathyroid glands in disease associated with demineralization of the human skeleton J Bone & Joint Surg 15 142 1933
244 GUTMAN A B SWENSON P C AND PARSONS W B Differential diagnosis of hyperparathyroidism J A M A 103 87 1934
245 TERRY W I AND SEARLS H H Parathyroid preservation J A M A 89 966 1937
246 MAYO C H AND PLUMMER H W The Thyroid Gland Beaumont Foundation Lectures St Louis C V Mosby Co 1926
247 COWDRY E V Endocrinology and Metabolism 1 New York D Appleton & Co 1922 501
248 GOETSCH E Clinical tests for thyroid disorders In Endocrinology and Metabolism Ed Barker L F New York D Appleton & Co 1922

249 Biddle A The Internal Secretory Organ New York William Wood & Co 1913 31
250 Stambul J Mechanisms of Disease New York Froben Press 1932
251 Underhill F P and Blatherwick N R J Biol Chem 19 119 1914 Quoted by J Stambul
252 McClendon J F Iodine and the Incidence of Goiter Minneapolis University of Minnesota Press 1939
253 Lamphier T A and Wickman W Postoperative Thyroid Storm Postgrad Med 15 493-512 1954
254 Attie J N and Liebmutter M Diagnosis and treatment of hyperparathyroidism New York State J Med 54 2 1-2723 1954
255 Boussingault J B Recherches sur la cause qui produit le goiter dans les Cordilleres de la Nouvelle-Grenade Annales de Chimie et de Physique 48 41-69 1831
256 — Memoire sur les salines iodiferes des Andes Annales de Chimie et de Physique 54 163 167 1833
257 McClelland J Observations on goitre Tr Med & Phys Soc Calcutta 7 145-155 1835
258 Inglis J Treatise on English bronchocele with a few remarks on the use of iodine London Longman 1838
259 Grange J Analyses des eaux des terrains talqueux anthraxiferes et cretaces de la vallee de l'Isere Observations sur la cause du developpement du goitre et du rachitisme sur les terrains magnesiferes Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences 27 358-369 1848
260 McClelland J Sketch of the medical topography climate and soil of Bengal and the N W Provinces London John Churchill 1859 (viii + pp 148)
261 Lebour G A On the geological distribution of endemic goitre in England Med Times & Gaz 2 492 1881
262 Bircher H Der endemische Kropf und seine Beziehung zur Taubstummheit und zum Kretinismus Basle B Schwabe 1883
263 Stevenson L E The cause of goitre Lancet 2 1556 1895
264 — The water supply of Leicester Lancet 2 1727 1898
265 — On the occurrence of endemic goitre in Cumberland and Westmoreland Privately printed 1898 12 pp
266 Berry Sir J Geological and geographical distribution of goitre in England and Wales In Diseases of the Thyroid Gland and Their Surgical Treatment London J & A Churchill 1901 xvi 5-65
267 McCarrison Sir R Observation on endemic goitre in the Chitral and Gilgit valleys Medico-Chirurgical Tr 89 437-470 1906 Lancet 1 1110-1111 1906
268 — The etiology of endemic goitre Lancet 1 219-226 1913
269 Clark T and Pierce C Endemic goitre Its possible relationship to water supply Pub Health Rep 29 939-948 1914
270 Stiner O Die Verbreitung des endemischen Kropfes in der Schweiz nach neuren Ergebnissen der Rekruten Untersuchungen Schweizer Kropf Kommission Beilage zum Bulletin des eidgenossischen Gesundheitsamtes 6: 23-57 1924
271 Hercus C E Benson W N and Carter C L Endemic goitre in New Zealand and its relation to the soil iodine J of Hyg 24 312-402 1925
272 Stocks P Relation of goitre to altitude and geological formation In Goitre in the English school child Quart J Med 21: 223-275 1928

273 McCarrison Sir R The simple goitres London Bailliere Tindall & Cox 1928 xi + 106 pp

274 Turton P H I The distribution of simple goitre in Derbyshire Proc Roy Soc Med 26 1223–1266 1933

275 Allen R I Rose L and Rose E K Juvenile thyrotoxicosis Results of treatment in 30 cases Pediatrics 14 38–44 1954

276 Harington C The Thyroid Gland Its Chemistry and Physiology London Oxford University Press 1933

277 Wharton T Adenographia sive Glandularum Totius Corporis Descripto London S C imp Authoris 1656

278 De Quervain F Cretinism in West London M J 35 117–129 1930

279 Fodere F E Traite du goitre et du cretinisme Precede d un discours sur l influence de l air humide sur l entendement humain Paris Bernard an 1800

280 Riedel B M C L Chronic inflammation leading to iron hard tumor of the thyroid Verhandungen Der Deut Gesell chaft Fur Chieurgie 25 75 1896

281 Fogh Andersen P Hyperparathyroidism Frequency and Treatment Ugeskr laeger (Copenhagen) 116 796–801 1954

282 Bram Israel Exophthalmic goiter in patients past age 50 Comments based on a series of 322 cases Pennsylvania Med J 42 117 1938

283 — Exophthalmic Goiter Its medical treatment End results in 2600 cases Delaware State Med J 10 223 1938

284 Crile G W Clinical analysis of 20 000 operations on the thyroid gland with special reference to the end result Proc Internat Assemb Inter State Post Grad Med Assoc North America 5 392 1929 1930

285 Cutler M and Buschke F Cancer Its Diagnosis and Treatment Philadelphia W B Saunders Co 1938

286 Ewing J Neoplastic Diseases Philadelphia W B Saunders Co 1940

287 Garlock J H Retro-esophageal goiter Surg Gynec & Obst 62 616 1936

288 Ginsburg S The value and place of radium in the treatment of diseases of the thyroid gland Am J Roentgenol & Rad Ther 24 283 1930

289 Goette K Ueber Schadigung nach Bestrahlung von Morbus Basedowii Fort chr a d Rontgentrahlen 39 111 1929

290 Groover T A Christie A C and Merritt E A Treatment of hyperthyroidism by all method with a summary of the authors experience with roentgen therapy Am J Roentgenol 10 385 1923

291 — and others Roentgen irradiation in the treatment of hyperthyroidism A statistical evaluation based on 505 Cases J A M A 92 1750 1929

292 Harris J H Radiation treatment of hyperthyroidism Report of results at the Hospital of the University of Pennsylvania during the seven and one half year ending July 1 1934 Am J Roentgenol 38 179 1937

293 Holzknecht G Ueber die Rontgentherapie der basedowschen Krankheit Strahlentherapie 30 605 1928

294 Jackson A S and Freeman H E The effect of iodine in adenomatous goiter with special reference to toxic adenomas J A M A 106 1261 1936

295 Jenkinson E L and Hunter A F The value of irradiation in toxic goiter Collective Review Surg Gynec & Obst 66 1 1938

296 Loucks R E Clinical evidence of thyrotoxic control after radium therapy Am J Roentgenol 18 509 1927

297 Mayo C H and Mayo C W Pre iodine and Post iodine days A Review of 37,288 Cases of Goiter at the Mayo Clinic West J Surg 43 477 1935

298 MEANS J H AND LERMAN J The action of iodine in thyrotoxicosis with special reference to refractoriness. J A M A 104 969 1935

299 — HERTZ S AND LERMAN J Nutritional factors in Graves disease Ann Int Med 11 429 1937

300 MENVILLE LEON J The radiologic aspect of thyrotoxicosis Radiology 18 568 1932

301 PFAHLER G E AND THRUSH M C Exophthalmic goiter treated by roentgen rays Therap Gaz 22 179 1906

302 — A summary of the results obtained by the X ray treatment of exophthalmic goiter New York State Med J 88 781 1908

303 — AND ZULICK J D The treatment of exophthalmic goiter by means of the roentgen ray Am J Roentgenol 3: 63 1916

304 — New roentgenographic technic for the study of the thyroid Am J Roentgenol 8 81 1921

305 — The treatment of hyperthyroidism by roentgen rays Am J Electroth & Radiol 42 207-212 1924

306 — The roentgen ray treatment of goiter and hyperthyroidism Proc Connecticut State Med Soc 137 202-213 1929

307 — AND VASTINE J H Results of roentgen therapy in goiter Based upon observations in 400 Cases Am J Roentgenol 24 395 1930

308 — Irradiation in the treatment of hyperthyroidism Radiology 18 8 9 1932

309 — AND VASTINE J H Irradiation in the treatment of toxic goiter Tr Am A Study Goiter 177 185 1932

310 — The irradiation treatment of hyperthyroidism M Ann District of Columbia 2 99-104 1933

311 — Roentgen ray treatment of hyperthyroidism Radiology 34 43 1940

312 PORDES FRITZ The oligosymptomatic thyrotoxicoses and their treatment by roentgen rays Strahlentherapie 30 619 1928

313 SCHMIDT C R WALSH W S AND CHESKY V E Liver insufficiency in toxic goiter and its treatment Surg Gynec & Obst 73 513 1941

314 WALTER O M ANSON B J AND IVY A C The effect of X rays on the thyroid and parathyroid glands Radiology 16 52 1931

315 WILLIUS F A The heart in thyroid disease Ann Clin Med 1 269 1923

316 JAFFE R H Severe anemia of aplastic type associated with sclerosis of thyroid gland Arch Int Med 61 19 1938

317 THURMON F M AND THOMPSON W O Low basal metabolism without myxedema Arch Int Med 46 879 1930

318 HURXTHAL L M Blood cholesterol in thyroid disease Effect of treatment Arch Int Med 52 86 1933

319 MEANS J H HERTZ S AND LERMAN J Pituitary type of myxedema or Simmonds Disease masquerading as myxedema Tr A Am Physician 55 32 1940

320 LERMAN J AND STEBBINS H D The pituitary type of myxedema J A M A 119 391 1942

321 WILKINS L AND FLEISCHMAN W Hypothyroidism in Childhood Effect of withdrawal of thyroid therapy upon serum cholesterol Relationship of cholesterol basal metabolic rate weight and clinical symptoms J Clin Endocrinol 1 91 1941

322 LERMAN J AND SALTER W T The maintenance requirements of myxedema patients Clinical and chemical assay of commercial thyroid preparations J Pharm & Exper Therap 50 298 1934

323 MEYER A F AND FERGUSON E A Influence of blood extracts from normal goitrous and diabetic persons on the heart rate of the thyroidectomized rat Endocrinol 30 158 1942
324 RASMUSSEN H Influence of thyroid hormone on heart and circulation Experimental investigations in dogs Acta med Scandinav supp 115 1 1941
325 SALTER W T The Endocrine Function of Iodine Cambridge Harvard University Press 1940
326 ALTHAUSEN T L LOCKHART J C AND SOLEY M H New diagnostic test (Galactose) for thyroid disease Am J Med S 199 342 1940
327 LAHEY F H Activated and apathetic hyperthyroidism Their importance in cases of heart failure South Surgeon 1 36 1932
328 KOWALLIS G F HAINES S F AND PEMBERTON J Goiter with associated myasthenia gravis Report of three cases of exophthalmic goiter and one case of adenomatous goiter with hyperthyroidism Arch Int Med 69 41 1942
329 GAMMON C D HARVEY A M AND MASLAND R L On the nature of certain diseases of the voluntary muscle Biological Symposia 3 291 1941
330 NETHERTON E W Syphilis and thyroid disease with special reference to hyperthyroidism Am J Syph 16 479 1932
331 FRIEDGOOD H B Relation of sympathetic nervous system and generalized lymphoid hyperplasia to pathogenesis of exophthalmic goitre and chronic lymphatic leukemia Am J Med Sc 183 841 1932
332 THOMPSON W O Changing concepts in treatment of toxic goitre Endocrinol 30 1015 1942
333 HERTZ S MEANS J H AND WILLIAMS R H Graves disease with dissociation of thyrotoxicosis and ophthalmopathy West J Surg 49 493–498 1941
334 FRIEDGOOD H B Clinical applications of studies in experimentally induced exophthalmos of anterior pituitary origin J Clin Endocrinol 1 804 1941
335 BARKER M H AND WOOD W B JR Severe febrile iodism during treatment of hyperthyroidism J A M A 114 1029 1940
336 ROSE E Diagnosis and treatment of thyroid disease M Clin North America 26 1711–1737 1942
337 PFAHLER G E Diagnosis and X ray treatment of hyperthyroidism M Clin North America 26 1751–1770 1942
338 AUB J C HEATH W AND ROPES M Studies of calcium and phosphorus metabolism Effects of thyroid hormone and thyroid disease J Clin Investigation 7 97 1929
339 BELOT J AND LEDINE Valeur de traitements de la maladie de Grave Basedow Ann de Med 33 363–387 1933
340 BORAK J Die Rontgentherapie und die Organtherapie bei innersekretorischen Erkrankungen Strahlentherapie 20 263 1925
341 BOWER J O AND CELARK J H Resistance of the thyroid gland to the action of radium rays Am J Roentgen & Rad Ther 10 632 1923
342 BROWN N B AND PAGE I H The effect of oral iodide on serum butanol insoluble protein bound iodine in various species Circulation 10 714–720 1954
343 LIBBY D A AND MEITES J Aureomycin and thyroid gland Science 190 354 1954
344 DUFFY B WHEELER T NOVAK P AND EDWARDS H Comparison of thyroid function tests U S Armed Forces M J 5 995 1954
345 DE COURCY C B Cancer of the thyroid Evaluation of results in recent series J Internat Coll Surgeons 22 408–413 1954

346 Winship T and Chase W *Childhood thyroid carcinoma in Western Europe* Chir Neerland 5 253 1953
347 Balme B W Metastatic carcinoma of thyroid Lancet 1 812 1954
348 Ficarra B J New dosage form of iodine M Times 82 458–459 1954
349 — Riedel's struma M Times 82 926–928 1954
350 Major R H Classic Description of Disease Springfield Ill Charles C Thomas 1939
351 McGavack T H The Thyroid St Louis C V Mosby Co 1951
352 Hoskins R G The Biology of Schizophrenia New York W W Norton & Co 1946
353 Kraepelin L Lectures on Clinical Psychiatry III Ed New York Wm Wood & Co 1913
354 Clinton M Medical management of thyroid disorders New York State J Med 52 2770–2774 1952
355 Horn R C and Dull J A Carcinoma of the thyroid Ann Surg 139 35–43 1954
356 Madigan J I and King W F Radio Active Iodine and protein bound iodine M J Australia 1 801–14 1954
357 Rinkoff S Freid J Rosman I and Spring M Treatment of hyperthyroidism with radioiodine New York State J Med 54 2470–2473 1954
358 Libby D and Meith J Negative effects of antibiotics on thyroid gland Science 120 354 1954
359 Beahr O H Pemberton J De J and Black B M Nodular goiter and malignant lesions of the thyroid gland J Clin Endocrinol 11 1157 1165 1951
360 Bertelsen A Christensen F and Iselund A Carcinoma of the thyroid Contributions to its clinical picture histopathology treatment and prognosis Acta chir Scandinav 99 205–224 1949
361 Black B M Surgical treatment of carcinoma of the thyroid gland J Clin Endocrinol 9 1412–1428 1949
362 Broders A C Surgical pathology of the thyroid gland West Surg 48 620–632 1940
363 Cattell R B *A more optimistic approach to cancer of the thyroid* West Surg 54 444–451 1946
364 Cole W H Slaughter D P and Rossiter L J Potential dangers of nontoxic nodular goiter J A M A 127 883–888 1945
365 Cope O Dobyns B M Hamlin E Jr and Hopkirk J What thyroid nodules are to be feared? J Clin Endocrinol 9 1012 1022 1949
366 Crile G W Jr and Dempsey W S Indications for removal of nontoxic nodular goiter J A M A 139 1247–1251 1949
367 Dailey M E Soley M H and Lindsay S Carcinoma of the thyroid gland a clinical and pathologic study Am J Med 9 194–199 1950
368 Frazell E L and Duffy B J Jr Hurthle-cell cancer of the thyroid a review of forty cases Cancer 4 952–956 1951
369 Graham E A Malignant epithelial tumors of the thyroid with special reference to invasion of blood vessel Surg Gynec & Obst 39 781–790 1924
370 Hinton J W and Lord J W Jr Is surgery indicated in all cases of nodular goiter toxic and nontoxic? J A M A 129 605–606 1945
371 King W L M and Pemberton J De J So-called lateral aberrant thyroid tumors Surg Gynec & Obst 74 991–1001 1942

372 LAHEY F H HARE H F AND WARREN S Carcinoma of the thyroid Ann Surg 112 977–1005 1940
373 PEMBERTON J DE J Malignant disease of the thyroid gland A clinical consideration Ann Surg 87 369–377 1928
374 — Malignant lesions of the thyroid gland a review of 774 cases Surg Gynec & Obst 69 417–430 1939
375 POCHIN E E MYANT N B HILTON G HONOUR A J AND CORBETT B D The indications for radio iodine treatment of thyroid carcinoma Brit M J 2 1115–1121 1952
376 SCHLESINGER M J GARGILL S L AND SAXE I H Studies in nodular goiter I Incidence of thyroid nodules in routine necropsies in a nongoitrous region J A M A 110 1638–1641 1938
377 TRUNNELL J B MARINELLI L D DUFFY B J JR HILL R PEACOCK W AND RAWSON R W The treatment of metastatic thyroid cancer with radioactive iodine Credit and debits J Clin Endocrinol 9 1138–1152 1949
378 WEGELIN C Malignant disease of the thyroid gland and its relations to goitre in man and animal Cancer Rev 3 297–313 1928
379 FRIEDMAN G J GREENBERGER M F AND BRANDALEONE H Cases of hyperparathyroidism with severe nephrocalcinosis Some interesting industrial medical implications J A M A 156 597–599 1954
380 DOBYNS B M AND WILSON L A Substances that produce exophthalmos Mod Med 22 7 1954
381 CASTLEMAN B Atlas of tumor pathology Armed Forces Inst Path Washington D C Section IV Fas 16 1952
382 HOBLER R E Hyperparathyroidism New York State J Med 54 1455–1462 1954
383 FROHNER R N AND WOLCAMOT J C Primary hyperparathyroidism Five cases in one family Ann Int Med 40 765–773 1954
384 SALVESEN H A Relationship between parathyroids and bone disease Minerva Medicine (Italy) 45 1473–76 1954
385 ANDERSEN P Hyperparathyroidism Ugeskr laeger (Denmark) 116 796–801 1954
386 CATLOW C E Mediastinal parathyroid adenoma West J Surg 62 352–53 1954
387 CURTISS P H CLARK W S AND HERNDON C H Vertebral fractures resulting from prolonged cortisone and corticotropin therapy J A M A 156 467–469 1954
388 DICKSON J A AND HALL W L B Hurthle cell tumors of the thyroid J Internat Coll Surgeons 22 570–582 1954
389 DONIACH I Effects of radioactive iodine alone and in combination with methyl thiouracil and acetylaminofluorene upon tumor production in the rat's thyroid gland Brit J Cancer 4 223 1950
390 WILENSKY A O AND KAUFFMAN P A Hurthle cell tumors of the thyroid gland Surg Gynec & Obst 66 1 1938
391 BABER E C (a) Contributions to the minute anatomy of the thyroid gland of the dog Phil Tr London 166 557 1877 (b) Researches on the minute structure of the thyroid gland Phil Tr London 172 577 1881–82
392 ASKANAZY M Pathologisch anatomische Beitrage zur Kenntniss des Morbus Basedowii insbesondere uber die dabei auftretende Muskelerkrankung Deutsches Arch F klin Med 61 118 1898

393 Langhans T Ueber die epithelialen Formen der malignen Strume Arch F Path Anat 189 69 1907
394 Getzowa S The parathyroid gland Intrathyroid cell masses of the same and rest of the postbranchial body Virchows Arch F Path Anat u Physiol 188 181 1907
395 Hamperl H Onkocytes and the so-called Hurthle tumor Arch Path 49 563 1950
396 Goldenberg I Hurthle cell carcinoma Arch Surg 67 495 1953
397 Hurthle K A study of the secretory process of the thyroid gland Arch f d Ges Physiol 56 1 1894
398 Zechel G Observation on the follicle cycle and on the presence of the macro thyrocyte in the human thyroid Anat Rec 56 119–130 1933
399 Friedman N B Cellular involution in the thyroid gland J Clin Endocrinol 9 874 1949
400 Foote N B Identification of Tumors Philadelphia J B Lippincott Co 1948 p 200
401 Getzowa S Manual of Tumor Nomenclature and Coding Prepared by the Subcommittee of the Statistics Committee American Cancer Society New York 1951
402 Ward R When is a malignant goiter malignant? J Clin Endocrinol 9 1031 1949
403 Chesky V E Dreese W C and Hellwig C A Hurthle cell tumors of the thyroid gland A report on 25 cases J Clin Endocrinol 11 1535 1951
404 Frazell E L and Duffy B J Hurthle cell cancer of the thyroid A review of 40 cases Cancer 9 5 1951
405 Lahey F H Hare H I and Warren S Carcinoma of the thyroid Ann Surg 112 977 1940
406 — Surgery of the thyroid gland New England J Med 236 46 1947
407 McFee W F The surgical treatment of carcinoma of the thyroid gland Surg Clin North America 33 361 1953
408 Hamperl H Uber das Vorkommen von Onkocyten in verschiedenen Organen und ihren Geschwulsten (Mund peichildrusen Bauchspeicheldrus Epithelkor pachen Hypophyse Schilddurse Lileiter) Virchows Arch f Path Anat 298 327 1936
409 Coldberg R C Metastasizing goitre Brit J Surg 39 153 1951
410 Cole W H Slaughter D P and Majarakis J D Carcinoma of the thyroid gland Surg Gynec & Obst 89 349 1949
411 Pemberton J DeJ Malignant lesions of the thyroid gland Surg Gynec & Obst 69 417 1939
412 Frazell E L and Foote F W Jr The natural history of thyroid cancer J Clin Endocrinol 9 1023 1949
413 Bakay L Jr Parafollicular cell adenoma of the thyroid gland Arch Path 45 447 1948
414 Crile G W Jr Papillary tumors of thyroid and lateral aberrant thyroid origin Surg Gynec and Obst 69 39 1939
415 Fitzgerald P J Foote F W Jr and Hill R F Concentration of I[131] in thyroid cancer shown by radioautography A study of 100 consecutive cases showing relation of histological structures to the function of thyroid carcinoma Cancer 3 86 1950

416 Graham F A Malignant tumors of thyroid Epithelial types Ann Surg **82** 30 1925
417 King W L M and Pemberton J De J So called lateral aberrant thyroid tumors Surg Gynec & Obst **74** 991-1001 1942
418 Koletsky S Bonte F J and Friedell H C Production of malignant tumors in rats with radioactive phosphorus Cancer Research **10** 129 1950
419 Morrow W J Hurthle cell tumors of the thyroid gland in an infant Arch Path **40** 387 1945
420 Parmley C C and Hellwig C A Lymphadenoid goitre Its differentiation from chronic thyroiditis Arch Surg **53** 190 1946
421 Rawson R W Radioiodine in the treatment of thyroid disease Surg Gynec & Obst **96** 118 1953
422 Shaw R D Metastasizing goiter Brit J Surg **39** 153 1951
423 Ward R Relation of tumors of lateral aberrant thyroid tissue to malignant disease of the thyroid gland Arch Surg **40** 606 1940
424 Warren S The significance of invasion of blood vessels in adenoma of the thyroid gland Arch Path **11** 255 1931
425 — The classification of tumors of the thyroid Am J Roentgenol **46** 47 1941
426 — Tumors of the thyroid Bull New York Acad Med **23** 5 1947
427 — and Meissner W A A working pathologic classification of thyroid disease Surg Clin North America **33** 759 1953
428 Warthin A S The constitutional entity of exophthalmic goiter and so called toxic adenoma Ann Int Med **2** 553 1928
429 Williamson G S and Pearse I H The structure of the thyroid organ in man J Path & Bact **26** 459-469 1923
430 Wilson G The thyroid follicles in man The normal and pathological configuration Anat Rec **37** 31 1927
431 Pohlman M L Otolaryngologic factor (Exophthalmos) Mod Med **22** 110 1954
432 Dobyns B M and Wilson L A Substance that produces exophthalmos Mod Med **22** 7 1954
433 Trevor W and Pack C Treatment of metastatic cancer of thyroid South Surg **15** 10 1949
434 Trevor W Should the thyroid nodule be removed Current Medical Digest **21** 86-91 1954
435 Trevor W The Treatment of Thyroiditis *In* The Treatment of Cancer and Allied Diseases New York P B Hoeber Inc 1955
436 Crile G W Thyroiditis Diagnosis and therapy Ann Int Med **37** 519-24 1952
437 Cutler M Treatment of subacute thyroiditis with corticotropin J A M A **155** 650-651 1954
438 Clark D Nelson F and Raiman R J Subacute nonsuppurative thyroiditis treatment with cortisone J A M A **151** 551-552 1953
439 Stich M Steroid therapy of subacute thyroiditis New York State J Med **53** 30-34 1955
440 King B T and Rosellini I J Treatment of acute thyroiditis with thiouracil J A M A **129** 267 1945
441 Young T O Inflammatory disease of the thyroid gland Minnesota Medicine **23** 105-111 1940

442 Marshall S Meissner W A and Smith D Chronic thyroiditis New England J Med 238 758-60 1948

443 Ficarra B J Mental attitude of the cancer patient to his disease Am J Psychiat 105 301 1948

444 Schachter M Etude Clinico-Psychologique De Six Phobiques Extrait de L'Hygiene Mentale (Marseilles France) 9: 119-134 1946-47

445 Starr P and Liebhold Schueck R Treatment of hypothyroidism J A M A 155 732-36 1954

446 Nadler S Bloch T Hidalgo J and Nisbet R An evaluation of radioactive iodine therapeutics in thyrotoxicosis J Louisiana Med Soc 106 268-3 5 1954

447 Cunella G and Bonomini V So-called tuberculous Basedowism Giornale Medicina Clinica (Bologna) 35: 678-99 1954

448 McClintock J and Lyons J J Preoperative thyroid preparation with Itrumil New York State J Med 51 1633 1951

449 Abraham A Thyroid disease in persons with emotional disorders J Med Soc New Jersey 51 357-359 1954

450 Crile G W Jr et al Diagnosis and treatment of thyroiditis with ACTH Cleveland Clin Quart 19 219 224 1952

451 Werner S C Hamilton J and Franck I Some effects of ACTH on thyroiditis and myxedema Proceedings of the Second ACTH Conference Ed J R Mote 2 521 1950

452 Franklin M The treatment of hyperthyroidism Med Clin North America 1955

453 Lindsay S Dailey M and Jones M Histologic effects of various types of ionizing radiation on normal and hyperplastic human thyroid glands J Clin Endocrinology 14 1179-1218 1954

454 Ficarra B J Asphyxia secondary to aortic aneurysm New York State J Med 47 2462-2463 1947

455 Loeb L and Bassett R B Effect of hormones of anterior pituitary on thyroid gland in the guinea pig Proc Soc Exper Biol & Med 26 860 1929 Comparison of effect of various preparations of anterior pituitary gland on thyroid of guinea pig Proc Soc Exper Biol & Med 27 490 1930

456 Kendall E C The isolation in crystalline form of the compound containing iodine which occurs in the thyroid J A M A 64 2042 1915

457 Harington C R Chemistry of thyroxine Constitution and synthesis of desiodothyroxin Biochem J 20 300 1926

458 Plummer H S Interrelationship of function of the thyroid gland Oxford Med 13 839 1921 and J A M A 77 243 1921

459 VanMeter S D Shivers M O and Simpson W I Report of Committee on Classification of American Association for Study of Goiter West J Surg 39 947 1931

460 McClendon J F and Williams A Simple goiter as a result of iodine deficiency J A M A 80 600 1923 The distribution of iodine with special reference to goiter Physiol Rev 7 189 1927

461 McCarrison R Facts in relation to the genesis of goiter Brit M J 1 1 8 1922 The Simple Goiters London Bailliere Tindall and Cox 1928

462 Hellwig C A Geographic and experimental studies on the etiology of goiter J Kansas M Soc 34 289 1933 Experimental goiter functional chemical and histological studies Arch Path 19 364 1935

463 Marine D and Kimball O P The prevention of simple goiter in man J.A M A 77 1068 1921
464 Rienhoff W F Jr Involutional or regressive changes in the thyroid gland in cases of exophthalmic goiter Arch Surg 13 391 1926
465 Loeb L and Friedman H Exophthalmos produced by injection of acid extract of anterior pituitary gland of cattle Proc Soc Exper Biol & M 29 648 1932
466 Roger H and Garnier M La sclerose du corps thyroide chez les tuberculeux Comp Rend Soc de Biol 50 873 1898
467 Cole W H and Womack N A Thyroid gland in infections Preliminary report J A M A 90 1274 1928
468 Anderson E M The production of hyperplasia of the thyroid with hyperthyroidism in the albino rat Canad M A J 28 23 1933
469 Curtis G M Cole V V and Phillips F J The blood iodine in thyroid disease West J Surg 42 435 1934
470 Perkin H J and Lahey F H Level of iodine in blood Arch Int Med 65 882 1940
471 Means J H and Lerman J The action of iodine in thyrotoxicosis With special reference to refractoriness J A M A 104 969 1935
472 Aub J C Bauer W Heath C and Ropes M Calcium and phosphorus metabolism The effects of the thyroid hormone and thyroid disease J Clin Investigation 7 97 1929
473 Puppel I D Klassen K P and Curtis G M Calcium metabolism in thyroid disease West J Surg 48 374-399 1940
474 King B T A new and function restoring operation for bilateral abductor cord paralysis J A M A 112 814 1939
475 Cole W H Precautions in the treatment of thyrotoxicosis Ann Surg 113 752 1941
476 Naffziger H C Progressive exophthalmos associated with disorders of the thyroid gland Ann Surg 108 529 1938
477 — and Jones O W Jr The surgical treatment of progressive exophthalmos following thyroidectomy J A M A 99 638 1932
478 Clute H M and Lahey F H Thyroiditis Ann Surg 95 493 1932
479 Hashimoto H Zer Kentniss der lymphomatosen Veranderung der Schilddruse (Struma lymphomatosa) Arch f klin Chir 97 219 1912
480 McSwain B and Moore S W Struma lymphomatosa Surg Gynec & Obst 76 562 1943
481 Graham L A Malignant epithelial tumors of the thyroid Surg Gynec & Obst 39 781 1924 Malignant tumors of the thyroid Ann Surg 82 30 1925
482 Ward Robertson Malignant goiter A survey of geographical types Read at the Annual Meeting of the American Association for the Study of Goiter at Salt Lake City West J Surg 43 494 1935
483 McLean F C and Hasting A B Clinical estimation and significance of calcium ion concentration in the blood Am J M Sc 189 601 1935
484 Askanazy M Beitrage zur Knochenpathologie quoted by Moore J J and Lorimier A A Roentgenographic studies of parathyroid deossification Am J Roentgenol 31 496 1934
485 Mandl F Therapeutischer Versuch bei einem Falle von Ostitis Fibrosa Generalista Mittels Exstirpation eines Epithelkorperchentumors Zentralbl f chir 53 260 1926
486 Barr D P Bulger H A and Dixon H H Hyperparathyroidism J.A.M.A 92 951 1929

487 Hanson A M Hormone of parathyroid gland Changes in blood serum calcium of thyroparathyroidectomized dogs modified by bovine hydrochloric acid Minnesota Med 8 283 1925

488 Collip J B The extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium J Biol Chem 63 395 1925

489 Jaffe H L and Bodansky A Experimental fibrous osteodystrophy (Osteitis Fibrosa) in hyperparathyroid dogs J Exper M 52 669 1930

490 Cope O Surgery of hyperparathyroidism The occurrence of parathyroids in the anterior mediastinum and division of the operation into two stages Ann Surg 114 706 1941

491 De Courcy J L A new theory concerning the etiology of Riedel's struma Surgery 12 754 1942

492 Churchill E D and Cope O Parathyroid tumors associated with hyperparathyroidism Eleven cases treated by operation Surg Gynec & Obst 58 255 1934

493 MacBryde C M The treatment of parathyroid tetany with Dihydrotachysterol J A M A 111 304 1938

494 Wyngaarden J B Antithyroid drugs and acute thyroiditis New England J Med 245 706–707 1951

495 Brush B E and Altland J K Goiter prevention with iodized salt results of 0 cases J Clin Endocrinol 12 1380–1388 1952

496 Altland J K and Brock B E Goiter prevention in Michigan J Michigan State Med Soc 51 985–989 1952

497 Barker S B Mechanism of action of the thyroid hormone Physiol Review 31 205–4 1951

498 Kempeneers J Nizet E and Dumont L Action de la Thyroxine Sur La Tuberculose Experimentale de la Souris C R Soc Biol (Paris) 147 741–42 1953

499 Werner S C Pituitary thyroid relationship in normal and disordered thyroid states Postgrad Radio Program New York Acad Med Jan 1955

500 Salter W and McKay E A Iodine in blood and thyroid of man and small animal Endocrinology 11 492 1951

501 Chaney A L Improvements in determination of iodine in blood Indust Eng Chem 12 179 1940

502 D'Angelo S A et al Effect of goitrogen withdrawal on pituitary thyroid system of guinea pig Endocrinology 54 565 1954

503 Duffy B J and Howland J W Use of tapazole to increase I concentration in euthyroid patients J Clin Endocrinol 12 61 1952

504 Koerner K A Congenital goiter with exophthalmos and hyperthyroidism J Pediat 45 464 1954

505 Timpano P Acute epidemic goiter and sporadic simple goiter Policlinico (Rome) 61 947–50 1954

506 Stanbury J B et al Iodine-deficient human thyroid gland J Clin Endocrinol 12 191 1952

507 Kirkwood S Tyrosine iodinase an enzyme concerned with thyroidal and extra thyroidal metabolism of organically bound iodine Read Before Am Goiter Ass Meeting Boston April 1954

508 Gross R T Kriss J P and Spaet T H Goitrogenic and hematological effects of cobaltous chloride in patient with sickle cell anemia Pediatrics 15 284–290 1955

509 Laine W A Vainio J and Holopainen T L Effect of thyroidectomy in rheumatoid arthritis Ann Rheumat Dist (London) 13 250-251 1954
510 Sheets R F Sequential occurrence of thyroiditis and thyrotoxicosis J.A.M.A 157 139-143 1955
511 Hamilton H E Kirkendall W M and Barker S B Radioactive iodine uptake of thyroid and plasma bound iodine in subacute thyroiditis J Clin Investigation 29 819 1950
512 Trunnell J B Duffy B J Gowan J Peacock W Kirschner C and Hill R The distribution of radioactive iodine in human tissues Necropsy study in 9 patients J Clin Endocrinol 10 1007 1950
513 Williams R Towery B Jaffee H Rogers W et al Radiotherapeusis Am J Med 7 707 1949
514 Kreutzer F Miller L Soley M et al Histologic localization with radioactive iodine in some human thyroid diseases A M A Arch Surg 60 07 1950
515 Billion H Radioiod Zur Schilddrusenbehandlung Arzt Wschr 5 689-695 1950
516 Dobyns B Skanse B and Maloff F A method for the preoperative estimation of function in thyroid tumors etc J Clin Endocrinol 9 1171 1949
517 Allen H C and Goodwin W E The scintillation counter as an instrument for in vivo determination of thyroid activity Radiology 58 68 1952
518 Bauer F K and Goodwin W E Acne and gynecomastia following I[131] therapy for hyperthyroidism J Clin Endocrinol 11 1574 1951
519 Von Schuregk R Kunstliche Radioaktive Isotope In Physiologie Diagnostik und Therapie Berlin Springer Verlag 1953
520 Kriss J Carnes W and Gross R Hypothyroidism and thyroid hyperplasia in patients treated with cobalt J.A.M.A 157 117-121 1955
521 Loeb L and Bassett R B Effect of hormone of anterior pituitary on thyroid gland in the guinea pig Proc Soc Exp Biol & Med 26 860 1929
522 Aron M Action de la prehypophyse sur la thyroide chez le cobaye Compt Rend Soc de Biologique 102 682 1929
523 Collip J B Diabetogenic thyrotropic adrenotropic and parathyrotropic factors of the pituitary J A M A 104 916 1932
524 Burn J H and Ling H W Effect of pituitary extract and adrenalin on ketonuria and liver glycogen Quart J Pharm 2 1 1929
525 Weinstein M Roberts M and Hadda G M Thyroidectomy for struma lymphomatosa J Internat Coll Surgeons 22 726-732 1954
526 Black B M Surgical aspects of hyperparathyroidism Am Surgeon 20 1044-50 1954
527 Windeyer B W *Cancer of the thyroid and radiotherapy Brit J Radiol* 27 537-552 1954
528 Bennett J E Periodic unilateral exophthalmos A M A Arch Ophth 52 683-698 1954
529 Schaaf M and Kyle L Diagnosis of hyperparathyroidism Am J M Sc 228 262 68 1954
530 Gonzale F Evidence of the functional differentiation of the embryonic chick thyroid in tissue culture Texas Reports on Biology and Medicine 12 828-832 1954
531 Leighton J Studies on human cancer using sponge matrix tissue culture Papillary adenocarcinoma of the thyroid gland Texas Reports on Biology and Medicine 12 847-864 1954

532 CARPENTER E Differentiation of chick embryo thyroids in tissue culture J Exper Zoology 89: 407–31 1942
533 EBELING A H Action de l'epithelium thyroidien en culture pure sur la croissance des fibroblastes Soc Biol Compt Rend 90 1449–50 1924
534 TAUROG A TONG W AND CHAIKOFF I The monoiodotyrosine content of the thyroid gland J Biol Chem 184 83–97 1950
535 ANDES J E MORGANTOWN W A AND MYER A C Blood guanidine in patients with parathyroid deficiency and idiopathic tetany J Lab & Clin Investig 23 123–176 1937
536 CHANG H C Relation of tryptophane to thyroid activity in the white rat Am J Physiol 73: 275–286 1925
537 GREER M A The effect on endogenous thyroid activity of feeding desiccated thyroid to normal human subjects New England J Med 244 385–90 1951
538 MORGAN M F OLDHAM A K AND TROTTER W R The effect of exogenous thyroxine on radioiodine uptake in normal subjects and in cases of thyrotoxicosis in remission J Endocrinol 8 250–53 1952
539 STARR P AND LIEBHOLD-SCHUECK R R A theory of thyroid hormone action derived from the differences in the effect of sodium levo thyroxine sodium dextrothyroxine triiodothyronine and potassium iodide on the uptake of radioactive iodine by the thyroid gland of normal human subjects Tr A Am Physicians 66 9–113 1953
540 WERNER S C HAMILTON H AND NEMETH M Graves disease hyperthyroidism or hyperpituitarism J Clin Endocrinol 12 1561–1 1952
541 WERNER S C AND HAMILTON H Pituitary thyroid relation Lancet I 96–97 1953
542 — Euthyroid patients with early eye signs of Graves disease Their response to L-triiodothyronine and thyrotropin Am J Med 18 608–612 1955
543 LERMAN J The physiologic activity of L-triiodothyronine J Clin Endocrinol 13 1341–46 1953
544 GREER M A AND SMITH G E Method for increasing the accuracy of the radio-iodine uptake as a test for thyroid function by the use of desiccated thyroid J Clin Endocrinol 14 1374–84 1954
545 MACGREGOR M E AND WHITEHEAD T P Pseudo-hypoparathyroidism etc Arch Diseases Childhood 29 398–416 1954
546 TAYLOR S Calcium as a goitrogen J Clin Endocrinol 14 1412–22 1954
547 SLOAN L W Of the origin characteristics and behavior of thyroid cancer J Clin Endocrinol 14 1309–1335 1954
548 HELLSTROM J Hyperparathyroidism Nord Med (Stockholm Sweden) 53 615–61 1955
549 STARR PAUL Hypothyroidism—An Essay on Modern Medicine Springfield Ill Charles C Thomas 1954
550 WERNER S C AND SPOONER M A new and simple test for hyperthyroidism employing L-triiodothyronine and the twenty four hour I[131] uptake method Bulletin of the New York Acad Med 31 13–145 1955
551 SCHILLING J A Struma fibrosa and thyroiditis Surg Gynec & Obst 81 533–550 1945
552 LAHEY F H Thyroiditis Its differentiation from malignancy Lahey Clin Bull 3 194–6 1944
553 LEE C N AND MCGRATH F J Struma Hashimoto Survey of literature Surgery 2 238–246 1937

554 I EG LARSEN N AND MALM O J Physiology of Calcium Metabolism Physiol Rev 33 424 1953
555 DRAKE T G ALBRIGHT F BAUER W AND CASTLEMAN B Chronic idiopathic hypoparathyroidism Report of six cases with autopsy findings in one Ann Int Med 12 1751 1939
556 SUTPHIN A ALBRIGHT F AND McCUNE D J Five cases (Three in siblings) of idiopathic hypoparathyroidism associated with moniliasis J Clin Endocrinol 3 625 1943
557 ALBRIGHT F BURNETT C H SMITH P H AND PARSON W Pseudohypoparathyroidism An example of Seabright Bantam Syndrome Report of three cases Endocrinol 30 929 1942
558 COSGROVE K F AND LATOURETTE K A Multiple myeloma simulating hyperparathyroidism Am J Med 15 862 1953
559 WILLIAMS R H (Ed) Textbook of Endocrinology Philadelphia W B Saunders Co 1950
560 FERTMAN M B AND CURTIS G M Foods and the genesis of goiter J Clin Endocrinol 11 1361-82 1951
561 HERTZ J On Goiter & Allied Disease London Oxford University Press 1943
562 NECKSTROTH C V AND CURTIS G M Criteria for therapy of malignant thyroid lesions with I A M A Arch Surg 67 187-93 1953
563 CURF L H Unilateral vocal cord paralysis J A M A 151 990 1953
564 CASTIGLIONI A A History of Medicine New York A Knopf Co 1947
565 HOSKINS R G Endocrinology New York Norton & Co 1941
566 HAMBLEN L C Endocrinology of Women Springfield Ill C Thomas Co 1945
567 FERRER F I AND McGAVACK T Thyroid J Clin Endocrinol 11 759 1951
568 BENDA C I Mongolism and Cretinism New York Grune & Stratton 1946
569 DONNISON C I Civilization and Disease Baltimore W Wood Co 1938
570 HAMLISCH R L Disorders of calcium and phosphorus metabolism their differential diagnosis Med Times 83 139-155 1955
571 LEIRBACK C W Use of I in thyroid disease Med Times 83 165-168 1955
572 PERLOFF W H Hirsutism—A manifestation of juvenile hypothyroidism J A M A 157 651-652 1955
573 MACGREGOR A G AND SOMNER A R The antithyroid action of para amino salicylic acid Lancet 2: 931-36 1954
574 JUSTIN BESANCON L KLOTZ H BARBIER P ET AL Study of phosphaturia induced by calcium infusion New test of parathyroid function Ann Endocrinol 15 405-424 1954
575 McDERMOTT W V HAMLIN E JR AND COPE O Cancer of the thyroid J Clin Endocrinol 14 1336 1954
576 BEIERWALTES W H Response to thyroid J Clin Endocrinol 15 148-150 1955
577 BER A Hyperkeratosis and Hypothyroidism Acta Endocriologia 16 505 1954
578 ANDERSEN H ASBOEHANSEN G AND QUAADE F Histopathologic examination of the skin in diagnosis of myxedema in children J Clin Endocrinol 15 459-468 1955
579 LEVENE M B ANDREWS G A AND KNISELY R M Large Doses of I in Dogs Radiation Dosage Correlated With Histologic and Autoradiographic changes Am J Roentgenol 73 88-97 1955
580 BAIRD I M GRAINGER R AND ROWLANDS B C Hyperparathyroidism due to parathyroid adenoma Brit J Surg 42 140-51 1954

581 Fauvert R., and Nicollo S Treatment of hyperthyroidism with radioactive iodine Semaine Hôpital, Paris 30 4266 1954
582 Marshall, S E, and Meissner, W A Struma Lymphomatosa Ann Surg 141 737-46 1955
583 Franklin M Treatment of Hyperthyroidism Med Clin North America 39 55-64 1955
584 Wyte M C Use of Thyrotropin (TSH) Clinical Investigation Service Armour Laboratories Illinois Personal Communication
585 Barnizer, L G Primary Hyperparathyroidism Ann Surg 141 725-36 1955
586 Pugh D G The Roentgenologic Diagnosis of Hyperparathyroidism Surg Clin North America, 32 1017 1952
587 Zieve, L, Sklar E, B, and Schultz, A L Comparative Value of BMP, protein-bound Iodine and Radioactive Iodine in Diagnosis of Borderline Hyperthyroidism J Lab & Clin Med 45 251-55 1955
588 Weihl, C Thyroid Disorders In Childhood Ohio Med Journ, 50 1044-47 1954
589 Weinberg M Carcinoma of Thyroid in Children So African J Clin Science 5 179-205 1955
590 Coindet J R Memoire sur un nouveau remede Contre le goitre Geneva 1820
591 Oswald A 3 5 Diiodotyrosin aus Jodeiweiss Ztschr für Physiol Chem 70 310 1911
592 Means J H Historical Background of the Use of Radioactive Iodine In Medicine New England J Med 252 936-40 1955
593 Rowland L P, Korengold M C, Jaffe, I A, Berg L, and Shy G M Prostigmine-induced muscle weakness in myasthenia gravis patients Neurology 5 89-99 1955
594 Buckwalter, J A, and Meredith L K Small cell carcinoma of the thyroid gland of youth Pediatrics 15 317-321 1955
595 Lahey F H, and Hoover W Injury to recurrent laryngeal nerves following thyroidectomy Their management and avoidance Ann Surg 108 545-562, 1938
596 Bartels E Hyperthyroidism—evaluation of treatment with antithyroid drugs followed by subtotal thyroidectomy Ann Int Med 37 1123-1134 1952
597 Swinton N Postoperative parathyroid tetany New England J Med 217 165-169 1937
598 Nafe, C A Metabolic disturbance following thyroidectomy West J Surg 48 253-260 1940
599 Wilcox W D, and Mayo C W Postoperative myxedema Surgery 7 117-121 1940
600 Ranke, E J, and Holinger, P H Paralysis of vocal cords following thyroidectomy J.A.M.A., 158 543-547 1955
601 Buckwalter, J A, Soper, P T, Davies, J, and Mason E E Postoperative hypoparathyroidism Surg, Gynec & Obst, 101 657-666 1955
602 Fuhr, W H, Kelly T R, and Krabill, W S Intrathoracic goiter Ann Surg, 142 235-247 1955
603 Gross S Granulomatous thyroiditis A.M.A. Arch Path, 59 412-418 1955
604 Mertens H G Course of myasthenia after denervation of the carotid sinus Nervenarzt 26 150-54, 1955 (Berlin, Germany)
605 Klinck, G H Thyroid hyperplasia in young children J.A.M.A., 158 1347-1348 1955

606 JAIMET C H AND THODE H G Thyroid function studies on children receiving cobalt therapy J.A.M.A 158 1353–1355 1955
607 SCAZZIGA B R BARBIERI L AND BERAND T Thyroid function in disorders of hepatic parenchyma Schweiz Med Wschnschr 85 471–77 1955
608 SPRINGER K C Lingual thyroid A.M.A Arch Otolaryng 61 386–93 1955
609 BLOCK MICHEL H Aberrant Lateral Thyroid Gland Semaine Hop Paris 31 3863–3869 1955
610 CHAPMAN E M AND MALOOF F Use of radioactive iodine in diagnosis and treatment of hyperthyroidism Medicine 34 261–321 1955
611 CLARK D E AND RULE J H Radioactive iodine or surgery in treatment of hyperthyroidism J A M A 159 995 997 1955
612 KUTCHERA AICHBERGEN H Thyroid and exophthalmos Wien Med Wchnschr 105 568 1955
613 HUNTER A R Chlorpromazine in thyroid crisis Lancet 2 173–174 1955
614 NEWBURGER R A SILVER S YOHALEM S B AND FEITELBERG S Uptake and blood level of radioactive iodine in hyperthyroidism New England J Med 253 127–130 1955
615 JAFFE H L ROSENFELD M H POBIRS F W AND STUPPY L J Radioiodine treatment of euthyroid cardiac disease J.A.M.A 159 434–439 1955
616 SITTIG H Use of active vegetable substance in preparing patients with thyrotoxicosis Munchen Med Wchnschr 97 826–832 1955
617 SILVER S YOHALEM S AND NEWBURGER R Pitfalls in diagnostic use of radioactive iodine J.A.M.A 159 1–5 1955
618 McCLINTOCK J Significance of nodular goiter Virginia Med Monthly 82 299–301 1955
619 HODGES R EVANS T C BRADBEERY J AND KEETTEL W C Accumulation of radioactive iodine by human fetal thyroids J Clin Endocrinol 15 661–667 1955
620 WERNER S C SPOONER M AND HAMILTON H Further evidence that hyperthyroidism is not hyperpituitarism J Clin Endocrinol 15 715 1955
621 GOLDMAN L Unusual manifestations of hyperparathyroidism Surg Gynec & Obst 100 675–89 1955
622 WERNER S C Euthyroid patients with early eye signs of Graves disease Their responses to L-triiodothyronine and thyrotropin Am J Med 18 608–612 1955
623 SUERMONDT W F Hyperparathyroidism Arch Chir Neerl 7 1–16 1955
624 PICARD R ET AL Hypertrophic muscular dystrophy associated with acquired thyroid insufficiency etc Semaine Hop Paris 31 1553 1955
625 STARR P Thyroxine therapy in preventive geriatrics J Am Geriatrics Soc 3 217–225 1955
626 TODD E Nodular goiter and carcinoma of thyroid J Kentucky Med A 53 316–19 1955
627 HENRIE J N NELSON R M AND CASTLETON K B Hyperparathyroidism Am Surg 21 403–418 1955
628 FOJANINI G AND CONTI A Postoperative crises of patients with hyperthyroidism Arch Ital Chir 79 29–59 1955
629 SPRINGER K C Linqual Thyroid Two cases in siblings diagnosed and treated with radioactive iodine A.M.A Arch Otolaryng 61 386–393 1955
630 PERLMUTTER M Use of thyroid hormone to differentiate between hyperthyroidism and euthyroidism J A M.A 158 718–720 1955
631 GROSSO O F AND LASERO P Problems of Aberrant Lateral Thyroid Tumors

632 MORGAN A D AND MACLAGAN N I Renal disease in hyperparathyroidism Am J Path **30** 1141-1168 1954
633 LI M C ET AL Thyroid function following hypophysectomy in man J Clin Endocrinol **15** 1278 1955
634 CLEMENTS F W Thyroid blocking agent as a cause of endemic goiter in Tasmania Med J Australia **2** 369-371 1955
635 KUNSTADTER R H AND STEIN A I Treatment of thyrotoxic children with thiourea derivatives long term follow up and recent experiences Am J Dis Children **90** 373-380 1955
636 LEE C M MCEDHEVNEY W T AND GALL E Unusual manifestations of parathyroid adenoma A M A Arch Surg **71** 475-485 1955
637 NOVAES A S Sarcoma of thyroid gland Rev Paulista Med **47** 70-82 1955
638 SKAUSE B Determination of protein bound iodine in serum in evaluation of thyroid function Nord Med **54** 1419-1423 1955
639 LOGALDO E Hydatid cyst associated with goiter Rev Asoc Med Argentina **69** 286-288 1955
640 ALBEAUX FERNET M AND ROMANI J D Malignant Edematous Exophthalmos Semaine Hop Paris **31** 3144-53 1955
641 — GUIOT J BRAUN S AND ROMANI J D Results of surgical hypophysectomy in a case of malignant edematous exophthalmos J Clin Endocrinol **15** 1239-46 1955
642 KLOTZ H P AND LUMBROSO P Return to neurothyroid concept of Basedow's disease Semaine Hop Paris **31** 3430-33 1955
643 BLOCK MICHEL H Aberrant lateral thyroid gland Semaine Hopital Paris **31** 3863-69 1955
644 OTTAVIANI P AND BORGHETTI A Reserpine in treatment of Flajani Basedow's disease Giornale Clin Med **36** 1337-54 1955
645 SABBATINI C Contribution to study of tumors in aberrant thyroid Reforma Medicine **69** 1350-58 1955
646 TURNER H H AND HOWARD R B Goiter from prolonged ingestion of iodide J Clin Endocrinol **16** 141-45 1956
647 DECOURT J DOUMIC J M MICHARD J P AND LOUCHATT J P Effect of cortisone and ACTH on edematous Basedowian exophthalmos Semaine Hopital Paris **32** 186-200 1956
648 VAN WYK J J GRUMBACH M M SHEPARD T H AND WILKINS L The treatment of hyperthyroidism in childhood with thiouracil drug Pediatrics **17** 221-29 1956
649 WERNER S C The Thyroid New York Paul B Hoeber Inc 1956
650 CHAPMAN E M AND MALOOF F Bizarre clinical manifestations of hyperthyroidism New England J Med **254** 1-5 1956
651 CATZ B AND STARR P Cancer of the thyroid with metastases to the lungs J A M A **160** 1046-1047 1956
652 BELLAMY J AND WHITE A Thyrotoxicosis New York State J Med **56** 1484-1486 1956
653 SCHULTZ A L AND ZILVE L Alterations in thyroid I uptake BMR following treatment with radioactive iodine Am J Med **20** 30-41 1956
654 CRILE G JR Queries and Minor Notes J A M A **160** 1200 1956
655 GARRISON F H History of Medicine Philadelphia W B Saunders Co 1922
656 LIDZ T AND WHITEHORN J C Life situations emotions and Graves disease In *Life Stress and Bodily Disease* 1135 pp Baltimore Williams & Wilkins Company 1950 Pp 445-450

657 Ham G C Alexander F and Carmichael H T Dynamic aspects of personality features and reactions characteristic of patients with Graves disease In *Life Stress and Bodily Disease* 1135 pp Baltimore Williams & Wilkins Company 1950 Pp 451-457
658 Lidz T and Whitehorn J C Psychiatric problems in thyroid clinic J A M A 139 698-701 1949
659 Starr P and Pomerenze H Therapeutic studies in hyperthyroidism Ann Int Med 15 226-243 1941
660 Foreign Letter Paraoxypropiophenone powerful synthetic hypophyseal inhibitor J A M A 145 341 1951
661 Paulsen C A Mortimore G E and Heller C G Pituitary action and estrogenic effect of parahydroxypropiophenone J Clin Endocrinol 11 892-894 1951
662 Thompson W O and Thompson P K Treatment of toxic goiter by irradiation of pituitary J Clin Investigation 23 951 1944
663 Boas N F and Ober W B Hereditary exophthalmic goitre—report of eleven cases in one family J Clin Endocrinol 6 575-588 1946
664 Chapman L M Corner G W Jr Robinson D and Evans R D Collection of radioactive iodine by human fetal thyroid J Clin Endocrinol 8 717-720 1948
665 Astwood E B Use of antithyroid drugs during pregnancy J Clin Endocrinol 11 1045-1056 1951
666 Davis L J and Forbes W Thiouracil in pregnancy effect on foetal thyroid Lancet 2 740 742 1945
667 Means J H Nature of Graves disease with special reference to ophthalmic component Am J M Sc 207 1-19 1944
668 Dobyns B M Present concepts of pathologic physiology of exophthalmos J Clin Endocrinol 10 1202-1230 1950
669 Barrett H W Goodman I and Dittmer K Synthesis of 5 halogeno 2 thiouracil and 6 methyl 5 halogeno 2 thiouracil derivatives J Am Chem Soc 70 1753-1756 1948
670 Williams R H Towery B T Rogers W F Jr Tagnon R and Jaffe H Antithyroid action of 5 iodothiouracil 6 methyl-5 iodothiouracil thiocytosine and (Ca) 4 n propyl-6 oxypyrimidyl 2 mercaptoacetic acid J Clin Endocrinol 9 801-817 1949
671 McClintock J C and Lyons J J A Clinical use of iodothiouracil New antithyroid compound New York State J Med 51 1633-1636 1951
672 Catz B Petit D W and Starr P Therapeutic studies in hyperthyroidism sodium 5 iodo 2 thiouracil J Clin Endocrinol 11 9 8-995 1951
673 Gassner F X Hopwood M I Herrold E A and Plummer A J Interpretation of goitrogenic properties of certain antithyroid agents J Clin Endocrinol 10 1485-1498 1950
674 Bielschowsky F Tumours of thyroid produced by 2 acetyl amino fluorene and allyl thiourea Brit J Exper Path 25 90-95 1944
675 Hinton J W and Lord J W Is surgery indicated in all cases of nodular goiter toxic and non toxic? J A M A 129 605 1945
676 Payne R L Crane A R and Price J G Thiouracil and carcinoma of thyroid Surgery 22 496-501 1947
677 Lahey F H Bartels E C Warren S and Meissner W A Thiouracil—use in preoperative treatment of severe hyperthyroidism Surg Gynec, & Obst 81: 425-439 1945

678 Curti, G. M., and Swenson, R. L. Thiouracil and its allies in treatment of hyperthyroidism: experimental and clinical survey. Internat. Abstr. Surg. **86**: 105–123, 1948.

679 Cattell, R. B. Surgical treatment of hyperthyroidism. J. Clin. Endocrinol. **9**: 999–1006, 1949.

680 Cole, O., Dobyns, B. M., Hamlin, E., Jr., and Hopkirk, J. What thyroid nodules are to be feared? J. Clin. Endocrinol. **9**: 1012–1022, 1949.

681 Beahrs, O. H., Pemberton, J. de J., and Black, B. M. Nodular goiter and malignant lesions of thyroid gland. J. Clin. Endocrinol. **11**: 1157–1165, 1951.

682 Rawson, R. W., et al. Effect of iodine on thyroid gland in Graves' disease when given in conjunction with thiouracil—[illegible] action theory of iodine. J. Clin. Investigation **24**: 869–877, 1945.

683 Wolff, J., and Chaikoff, I. L. Inhibitory action of excessive iodide upon synthesis of diiodotyrosine and of thyroxine in thyroid gland of normal rat. Endocrinology **43**: 174–179, 1948.

684 Hertz, S., and Roberts, A. Application of radioactive iodine in therapy of Graves' disease. J. Clin. Investigation **21**: 624, 1942.

685 Hamilton, J. G., and Lawrence, J. H. Recent clinical developments in therapeutic application of radio-phosphorus and radio-iodine. J. Clin. Investigation **21**: 624, 1942.

686 Hertz, S., and Roberts, A. Radioactive iodine in study of thyroid physiology. VII. Use of radioactive iodine therapy in hyperthyroidism. J.A.M.A. **131**: 81–86, 1946.

687 Chapman, E. M., and Evans, R. D. Treatment of hyperthyroidism with radioactive iodine. J.A.M.A. **131**: 86–91, 1946.

688 Soley, M. H., Miller, E. R., and Foreman, N. Graves' disease: treatment with radioiodine (I^{131}). J. Clin. Endocrinol. **9**: 29, 1949.

689 Werner, S. C., Quimby, E. H., and Schmidt, C. Clinical experience in diagnosis and treatment of thyroid disorders with radioactive iodine (8-day half life). Radiology **51**: 564–578, 1948.

690 Chapman, E. M., Skanse, B. N., and Evans, R. D. Treatment of hyperthyroidism with radioactive iodine. Radiology **51**: 558–563, 1948.

691 Crile, G., Jr. Practical Aspects of Thyroid Disease. 553 pp. Philadelphia: W. B. Saunders Company, 1949. Pp. 106–112.

692 Soley, M. H., and Foreman, N. Radioiodine therapy in Graves' disease: review. J. Clin. Investigation **28**: 1367–1374, 1949.

693 Crile, G., Jr. Treatment of tumors of thyroid with divided doses of radioactive iodine. Am. J. Roentgenol. **65**: 415–419, 1951.

694 Marinelli, L. D., Trunnell, J. B., Hill, R. F., and Foote, F. W. Factors involved in experimental therapy of metastatic thyroid cancer with I^{131}: preliminary report. Radiology **51**: 553–557, 1948.

695 Trunnell, J. B., et al. Treatment of metastatic thyroid cancer with radioactive iodine: credits and debits. J. Clin. Endocrinol. **9**: 1138–1152, 1949.

696 Nickson, J. J. Dosimetric and protective considerations for radioactive iodine. J. Clin. Endocrinol. **8**: [illegible]21–[illegible]31, 1948.

697 Brues, A. M. Biological hazards and toxicity of radioactive isotopes. J. Clin. Investigation **28**: 1286–1296, 1949.

698 Cahan, W. G., et al. Sarcoma arising in irradiated bone: report of 11 cases. Cancer **1**: 3–29, 1948.

699 Auerbach, O., Friedman, M., Weiss, L., and Amory, H. I. Extraskeletal osteogenic sarcoma arising in irradiated tissue. Cancer **4**: 1095–1106, 1951.

700 SITTZ S AND HIGINBOTHAM N L Osteogenic sarcoma following prophylactic roentgen ray therapy report of case Cancer 4 1107–1112 1951
701 SCHULZ M D AND ROBBINS L L Dangers of irradiation of hypertrophied lymphoid tissue of the nasopharynx Tr Am Acad Ophth 1949 Pp 243–253
702 EVANS R D Quantitative aspect of radiation carcinogenesis in humans Unio Internat Contra Cancrum ACTA 6 1229–1237 1950
703 HAINES S F KEATING F R JR POWER M H WILLIAMS M M D AND KELSEY M P The use of radioiodine in the treatment of exophthalmic goiter J Clin Endocrinol 8 813–825 1948
704 HENSHAW P S RILEY E F AND STAPLETON G E Plutonium project biologic effects of pile radiation Radiology 49 349–359 1947
705 QUIMBY E H AND WERNER S C Late radiation effects in roentgen therapy for hyperthyroidism their possible bearing on use of radioactive iodine J A M A 140 1046 1949
706 ASTWOOD E B Treatment of hyperthyroidism with thiourea and thiouracil J A M A 122 78–81 1943
707 ASTWOOD E B SULLIVAN J BISSELL A AND TYSLOWITZ R Action of certain sulfonamides and of thiourea upon function of thyroid gland of rat Endocrinology 32 210–225 1943
708 MOORE F D SWEENEY D N JR COPE O RAWSON R W AND MEANS J H Use of thiouracil in preparation of patients with hyperthyroidism for thyroidectomy Ann Surg 120 152–169 1944
709 HIMSWORTH H P Thiouracil and its derivatives in routine treatment of thyrotoxicosis Brit M J 2 61–64 1948
710 ASTWOOD E B AND VANDERLAAN W P Treatment of hyperthyroidism with propylthiouracil Ann Int Med 25 813–821 1946
711 BARTELS E C Propylthiouracil its use in preoperative treatment of severe and complicated hyperthyroidism Tr Am A Study Goiter 1947 Pp 89–98
712 ASTWOOD E B Use of antithyroid drugs in treatment of hyperthyroidism Tr Am A Study Goiter 1949 Pp 210–212
713 HIMSWORTH H P MORGANS M E AND TROTTER W R Thyroidectomy and thiouracil in toxic goitre interim comparison Lancet 1 241–243 1947
714 BARTELS E C Thiouracil and allied drugs in hyperthyroidism New Eng J Med 238 6–11 1948
715 MORGANS M E AND TROTTER W R Seasonal variations in thyrotoxicosis Lancet 2 1083 1949
716 MCCULLAGH E P HUMPHREY D C MCGARVEY C J AND SUNDGREN V Results of propylthiouracil therapy for hyperthyroidism J A M A 147 106–110 1951
717 IVERSEN K Late results from continuous treatment of thyrotoxicosis with methylthiouracil J Clin Endocrinol 11 298–311 1951
718 HAZARD T P AND EDDY R E Modification of sexual cycle in brook trout (*salvelinus fontinalis*) by control of light Tr Am Fisheries Soc 80 158–162 1951
719 STANLEY M M AND ASTWOOD E B Determination of relative activities of antithyroid compounds in man using radioactive iodine Endocrinology 41 66–84 1947
720 BONDY P K Treatment of hypocalcemic tetany GP 11 6–81 1955
721 DUFFY J AND HOWLAND J W Radioiodine Principles of diagnosis and treatment of thyroid disease New York State J Med 51 1399–1405 1951

22 POPPEN J Exophthalmos—Surgical treatment Am J Surg 64 64–9 1944
23 HOWE W E AND FOOTE M N Carcinoma of the thyroid gland Radiology 52 541–556 1949
24 FRIEDMAN G J GREENBERGER M E AND BRANDALEONE H Case of hyperparathyroidism with severe nephrocalcinosis some interesting industrial medical implications J A M A 156 597 599 1954
25 McCLINTOCK J C STRANAHAN A ALLEY R D AND BAKER W A Thoracocervical approach for malignant disease of the thyroid gland Ann Surg 139 158–165 1954
26 SCHACHTER M Étude clinico-psychologique de six phobiques L Hygiène Mentale 9 119–131 1946–1947
27 JOHNSON N Hemorrhage necrosis and cyst formation in the thyroid gland Surg Gynec & Obst 101 85 93 1955
28 Medical Forum on Hyperthyroidism Mod Med 23 182–190 1955
29 FRANKLIN M Treatment of hyperthyroidism Med Clin North America 39 55–64 1955
30 SIGERIST H R History of Medicine I Primitive and Archaic Medicine New York Oxford University Press 1951
31 McGAVACK T H The Thyroid St Louis C V Mosby Co 1951
32 KEYNES G Thymomas and myasthenia gravis investigation into thymic diseases and tumor formations Brit J Surg 62 449–462 1955
33 WEAVER J A JONES A AND SMITH R A Thyrotoxic coma Brit Med J 4957 20–23 1956
34 HOFFMAN E *Intrathoracic goiter Brit J Surg 43 310–314 1955*
35 HOWARD J E Metabolism of Calcium and Phosphorus in Bone Bull New York Acad Med 27 24 1951
36 BLACK B M Surgical Treatment of Hyperparathyroidism S Clin North America 32 1031 1952
37 BARTTER F C The Parathyroids Ann Rev Physiol 16 429 1954
38 ALB J C Relation between the Parathyroid and Phosphorus Metabolism in Phosphorus Metabolism (edited by W D McElroy and B Glass) II 626 Baltimore Johns Hopkins Press 1952
39 FASCHKIS K E RAKOFF A E AND CANTAROW A Clinical Endocrinology New York Paul B Hoeber Inc 1954
40 ALBRIGHT F AND REIFENSTEIN E C JR The Parathyroid Glands and Metabolic Bone Disease Baltimore The Williams & Wilkins Company 1948
40a SUGAR O Central Neurological Complications of Hypoparathyroidism A M A Arch Neurol & Psychiat 70 86 1953
41 DRAKE T G ALBRIGHT F BAUER W AND CASTLEMAN B Chronic Idiopathic Hypoparathyroidism Report of Six Cases with Autopsy Findings in One Ann Int Med 12 1751 1939
42 STEINBERG H AND WALDRON B R Idiopathic Hypoparathyroidism An Analysis of Fifty Two Cases Including the Report of a New Case Medicine 31 133 1952
43 HOWARD J E HOPKINS T R AND CONNOR T B On Certain Physiologic Responses to Intravenous Injection of Calcium Salts into Normal Hyperparathyroid and Hypoparathyroid Persons J Clin Endocrinol 13 1 1953
44 ELLSWORTH R AND HOWARD J E Studies on the Physiology of the Parathyroid Glands VII Some Responses of Normal Human Kidney and Blood to Intravenous Parathyroid Extract Bull Johns Hopkins Hosp 55 296 1934

745 ELRICK H ALBRIGHT F BARTTER I C FORBES A I AND REEVES J D Further Studies on Pseudo Hypoparathyroidism Report of Four New Cases Acta endocrinol 5 199 1950
746 RIVES J D Mediastinal Aberrant Goiter Ann Surg 126 797–810 (Nov) 1947
747 ELLIS F H JR GOOD C A AND SEYBOLD W D Intrathoracic Goiter Ann Surg 135 79–90 (Jan) 1952
748 LAHEY F H Surgical Management of Intrathoracic Goiter Surg Gynec & Obst 53 346–354 (Sept) 1931
749 LINDSKOG G AND GOLDENBERG I Differential Diagnosis pathology and treatment of substernal goiter J A M A 163 527–529 1957
750 LICARRA B J Biologic activity of thyroid cancer Roslyn Hosp Quart 2 3 1956

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